PHARMACOLOGY
AND
PHARMACOTHERAPEUTICS

Satoskar, Kale, Bhandarkar's

PHARMACOLOGY AND PHARMACOTHERAPEUTICS

SIXTH EDITION

Revised by

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PREFACE TO THE SIXTH EDITION

It is now nearly ten years since the publication of the first edition of this text book. The fifth edition was subsidised by the National Book Trust of India which made this book available to students at a much lower price. However, the publishers are now informed by the National Book Trust regarding the change in the policy which does not permit them to extend the subsidy to a book which has gone into more than three editions.

The new Sixth Edition has undergone a considerable amount of revision and is brought up-to-date. While doing so less dynamic or outmoded areas have been condensed or eliminated to allow adequate consideration of important pharmacological and therapeutic advances.

Special care has been taken by the authors and the publishers of this book to ensure that dosage recommendations are precise and in agreement with standards officially accepted at the time of publication. However, it may be noted that such drug schedules are often changed in the light of accumulating clinical experience and continuing laboratory studies. This is more true in the case of products introduced recently. We, therefore, urge the readers to refer to the manufacturers' recommendations for dosage, especially for the new drugs and for those used infrequently in clinical practice.

We are greatly indebted to many colleagues for their useful criticism and other help during the revision of this edition. Our special thanks are due to Professor S. M. Karandikar, Seth G. S. Medical College, Bombay for Fig. No. 14.7, Dr. V. R. Mehta, Hon. Professor of Dermatology, L. T. Municipal Medical College, Bombay for the section on "Principles of local treatment of skin lesions", Dr. S. D. Sule, M.D. for preparing the index and Dr. B. S. Kulkarni, Associate Professor of Biochemistry, Seth G. S. Medical College, Bombay for revising the Appendix B.

Finally, the authors would be grateful to receive any comments and suggestions regarding the material as well as the presentation in this edition.

Bombay,
December, 1977.

R. S. Satoskar
S. D. Bhandarkar

PREFACE TO THE FIRST EDITION

Pharmacology has undergone a phenomenal growth during the last twenty years and drug therapy now forms a major aspect of therapeutics. So far, pharmacology was traditionally associated with the study of drugs in dogs, cats and rats, while therapeutics or clinical application was regarded as an entirely independent and a mystical skill. Now it is generally agreed that the major object of teaching pharmacology to the medical students is to provide a rational basis for choosing and using drugs skilfully to relieve patients' ailments. This is becoming more and more important as the practising doctor is now confronted with so called "newer drugs" at such a great pace that even a full-time pharmacologist sometimes finds it difficult to keep abreast of their merits and demerits. It is highly desirable, therefore, that students of pharmacology should be educated to develop a critical outlook towards various drugs, as they are introduced. This means that the book on pharmacology meant for medical students should not only give detailed account of various pharmacological actions but should also furnish a critical appraisal of their present day use in therapeutics. We have attempted in this book to combine these two important aspects. In addition, an outline of experimental evaluation of drugs in animals and man is also provided. While doing this, it was thought essential to give the relevant information from other disciplines like physiology, pathology and clinical medicine. This, though a repetition to a certain extent, is no doubt useful to understand the basis of rational therapeutics. After all, pharmacology is in some respects a bridge between basic medical sciences on one hand and clinical medicine on the other. Most of the presently available text books, except a few classics written by many authors, fail to achieve this goal. It is a common experience of those who teach pharmacology in this country to find it difficult to recommend one single book to the undergraduate medical students. Many books which give excellent information about pharmacological actions treat the therapeutics very cursorily while others that give delightful therapeutics probably assume that students know most of the basic pharmacology. It is not practicable to recommend routinely the classical multi-author books to undergraduate students, as they have many other subjects to go through, which are equally important and advanced. This book is written to fill up this gap between a big book and a concise, less informative work, so that students will get all the necessary information by reading one book. While doing this, obviously we have to restrict the size of the book, lest it would be unwieldy and defeat the very purpose for which it is written. In order to achieve this, history and chemistry are reduced considerably while diagrams are included strictly to facilitate the understanding of the subject. The coverage is given according to the importance of the subject in therapeutics. Wherever multiple drugs of similar type are available, only the important prototype is discussed in detail, while others have received only a brief mention.

Although the book is written mainly for undergraduate medical students, it will also prove useful to post-graduates and practising doctors. The therapeutics part includes many details so that the book would continue to be useful even after passing pharmacology and is expected to serve as a pharmacotherapeutic reference work. The big multi-author books on this subject are no doubt excellent and authoritative but are not easily accessible to practising doctors at the time of emergency. In such circumstances this book should find its use.

The book is not written with an eye on examination' but it is the hope of the authors that by reading this book students would develop an attitude of thinking towards newer drugs which are many times made to appear like "therapeutic marvels". It is not expected that undergraduate students should 'cram' this book and try to remember everything that is given. It is neither possible nor necessary. They are expected to learn the basic pharmacology of the drugs in common clinical use and their rational application in therapeutics. However, the authors will feel rewarded, if students can grasp the ideology and spirit behind presentation of this book.

Drug therapy related to tropical problems is emphasized; this topic is often dismissed summarily in other works of this size. Proprietary names are included wherever necessary so that their pharmacological identity is recognised by the reader. No detailed reference list is given as this would have added many more pages. Instead, the books, reviews, symposia and monographs referred to are enlisted at the end of the book. The enthusiastic reader may refer to these for a more extensive reference list. Preparations included in the Indian Pharmacopoeia are marked as I.P. and those included in British Pharmacopoeia are listed in a separate list at the end.

It is not possible to present a book of such a size without generous help of others and the authors are deeply grateful to their many colleagues at Seth G. S. Medical College and Lokmanya Tilak Municipal Medical College, Bombay. Particularly, the help rendered by Drs. B. S. Kulkarni, S. M. Chittal, S. V. Gokhale, M. G. Wagh, C. H. Kewalramani, Mr. N. K. Dadkar, Mr. V. S. Jathar, Dr. S. M. Karandikar and Miss P. Mirwankar is gratefully acknowledged. We also would like to express our grateful thanks to many authors and publishers who promptly conceded our requests and granted permission to reproduce certain tables and diagrams, as indicated in the text. We are greatly indebted to Dr. A. F. Golwalla, Hon. Professor of Medicine, Seth G. S. Medical College and K. E. M. Hospital, Bombay for his encouragement and permission to reproduce E.C.G. records. Finally, our thanks are due to Popular Prakashan and Popular Press (Bom.) Pvt. Ltd., who as publishers and printers respectively are responsible for delivering this book in your hand expeditiously.

R. S. Satoskar
A. K. Kale
S. D. Bhandarkar

Bombay,
November, 1968.

Section X: Drugs Used in Disorders of the Gastrointestinal Tract

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Appetizers, Digestants, Carminatives, Appetite Suppressants and Agents Lowering Serum Cholesterol

Loss of appetite is a fairly common complaint in clinical practice. Its etiology is often vague and varies from such diverse causes as prolonged, debilitating illnesses to purely psychological disturbances. It is imperative, therefore, to investigate thoroughly an individual complaining of loss of appetite (anorexia); treatment of the underlying cause often improves the condition.

Anorexia due to worries and mental disturbances often responds satisfactorily to tranquillizer or placebo therapy. Symptomatically, appetite can often be improved by varying the diet and by use of such simple preparations as lemon pickles and soups; use of costly 'appetite stimulants' and 'tonics' for this purpose is unnecessary.

The agents employed commonly to stimulate appetite are :

(a) **Bitters:** It has been claimed that bitter substances reflexly augment the flow of gastric juice and increase appetite. Their appetite stimulating action, however, remains to be proved. The bitters often prescribed for this purpose include simple bitters like gentian, calumba, quassia and chirata. These are used as watery infusions or tinctures which, in addition to alcohol, contain flavouring agents such as tincture of orange peel or cardamom. The official bitter preparations are:

(i) Chirata I.P.: This is the plant *Swertia chirata*, collected when in flower and dried. It contains not less than 1.3 per cent of the bitter principle of chirata. It is a common household remedy in India.

(ii) Concentrated compound chirata infusion I.P. which contains dried chirata with dried orange and lemon peels and 25 per cent alcohol. Dose: 2 to 4 ml. by mouth.

(iii) Gentian U.S.P. is available as 10 per cent tincture of gentian with bitter orange peel and cardamom. Dose: 2 to 3 ml. by mouth.

The aromatic bitters combine the property of bitterness with that of an aromatic volatile oil—e.g. orange and cardamom.

(b) **Alcohol:** Alcohol in small quantities can augment the gastric secretion both reflexly by stimulation of the taste buds and by a direct action. It is one of the most important constituents of various popular 'tonics'. Various bitter mixtures contain 10-15 per cent of alcohol. Repeated ingestion of alcohol in high concentrations, however, causes chronic gastritis and a diminution in appetite.

(c) **Miscellaneous Compounds:** Insulin, on parenteral administration, augments gastric secretion by producing hypoglycemia. Small doses of insulin have been used to increase appetite; such type of therapy, however, is irrational, inconvenient and hazardous. Similar claims have been advanced for vitamin B_{12} and anabolic steroids but whether appetite stimulation is a primary action of these compounds or secondary to their metabolic effects, remains to be established. These compounds are discussed in detatil elsewhere. Two antihistaminics, buclizine and cyproheptadine, have also been claimed to possess appetite stimulating property. However, indiscriminate use of such drugs should be avoided, as cyproheptadine, a 5-HT antagonist, has been shown to inhibit the release of ACTH and depress the circulating cortisol level.

DIGESTANTS

The digestants are the drugs that are claimed to enhance the process of digestion in the gastrointestinal tract. The commonly used digestants are:

(a) HYDROCHLORIC ACID, DILUTE: Deficient secretion of hydrochloric acid or hypochlorhydria is present in approximately 10 to 15 per cent of the general population, while achlorhydria occurs in association with chronic gastritis, gastric malignancy and pernicious anemia. Hypochlorhydria may produce symptoms like diarrhoea, fullness of stomach after meals and belching. These symptoms may be relieved by the administration of dilute hydrochloric acid or other substances which form hydrochloric acid in the stomach. The preparations available are:

(i) Dilute hydrochloric acid I.P. is 10 per cent w/v hydrochloric acid. The preparation is usually diluted with 25 to 50 volumes of water and 4 to 6 ml. of the diluted solution are administered by mouth through a straw to prevent its effect on the teeth.

(ii) Glutamic acid hydrochloride and betaine hydrochloride, which form hydrochloric acid in the stomach, can also be used for a similar purpose.

(b) PEPSIN: This is a proteolytic enzyme, obtained from the glandular layer of the fresh stomach of the hog. It is administered orally in the dose of 0.5-1 g. It is of doubtful value except perhaps in patients with gastric achylia, a condition characterized by defective acid and pepsin secretion by the stomach. Gastric achylia is often encountered in patients with carcinoma of the stomach and pernicious anemia.

Another enzyme, papain, obtained from vegetable source (papaya) also has proteolytic properties.

(c) RENNIN: This is a partially purified milk-curdling enzyme, obtained from the glandular layer of calf stomach. It is employed for similar purpose as pepsin.

(d) PANCREATIN: This contains the enzymes amylase, trypsin and lipase and is obtained from hog or ox pancreas. It has been employed as a replacement therapy in chronic pancreatitis, obstruction caused by the cancer of the head of pancreas, cystic fibrosis and after pancreatectomy. It is not useful in gastro-intestinal disorders unrelated to pancreatic enzyme insufficiency. The drug is administered orally in the dose of 500 mg. in enteric coated capsules, to prevent its destruction by pepsin.

(e) BILE, BILE SALTS AND BILE ACIDS: Normally, about 1000 ml. of bile is secreted by the liver cells per day. Cholecystokinin, the polypeptide secreted by the duodenal mucosa, is the main chemical stimulant to biliary secretion. However, it is not available for therapeutic use. Bile salts increase the flow as well as the concentration of bile and hence, are termed *choleretics*. The bile salts and acids, however, do not increase the excretion of preformed bile pigments.

The available preparations include,

(i) Ox bile extract tablet. Dose: 300 mg. by mouth,

(ii) Dehydrocholic acid available as 250 mg. tablet. Dose: 500 mg. thrice daily, and

(iii) Sodium dehydrocholate injection, available as 20 per cent solution in 3 and 10 ml. ampoules. Dose: 3 to 5 ml. i.v.

(iv) Caerulein, a polypeptide, is claimed to be three times as powerful as cholecystokinins.

The bile salt preparations have been employed to facilitate surgical drainage, as replacement therapy in biliary fistulae, to promote flow of bile in diseases of biliary tract not associated with acute hepatitis, for removal of small biliary calculi along with antispasmodics like atropine, and for their choleretic effect in conditions like liver cirrhosis and functional hepatic insufficiency. Their therapeutic usefulness, however, is doubtful. Sodium dehydrocholate, given intravenously, was in the past employed for the measurement of circulation time.

CHENODEOXYCHOLIC ACID: This drug is believed to act by altering the ratio of cholesterol to bile salts in the bile, thus helping to dissolve gallstones and prevent their recurrence. The drug is administered orally in the dose of 0.5-1.0 g. daily. Larger doses cause diarrhoea. It is under evaluation.

(f) FLORANTYRONE: This is a synthetic agent structurally unrelated to bile salts. It stimulates the flow of bile. The bile is of low specific gravity and hence, the drug is termed *hydrocholeretic*. The adverse effects of the drug include gastrointestinal disturbances and changes in the liver function tests. Because it is a hydrocholeretic, it is contra-indicated in the presence of mechanical biliary obstruction, acute cholecystitis and severe hepatitis.

The drug is administered orally in the dose of 750 mg. to 1 g. per day. It has been claimed to be useful in chronic gall bladder dysfunction and in the post-cholecystectomy syndrome. These claims, however, need confirmation.

(g) TAKA DIASTASE: These enzymes are obtained from the fungus. *Aspergillus oryzae*, grown on wheat bran. They act on carbohydrate in *in vitro studies*. On the basis of this, the drug is recommended as a digestant. Its value in human therapeutics, however, is doubtful.

CARMINATIVES

These are the drugs used to expel gas from the stomach or the intestines in the treatment of flatulence and in colics. Most of these drugs are aromatic volatile oils. They act by mild irritation, thereby increasing the gastrointestinal motility and causing relaxation of sphincters. They produce a feeling of warmth in the stomach. They do not affect the gastric acid secretion significantly. Indian food contains enough carminatives in various spices and condiments. The common ones are cardamom seeds, ginger, fennel seeds, asafoetida, cinnamon bark, cloves, coriander, anise and nutmeg. Along with sodium bicarbonate, they form important constituents of various 'gripe water' mixtures popularly used in infants to reduce griping. Therapeutically, these volatile oils are used in the form of tinctures such as tinc. Card Co. and tinc. Zingiberis.

Although carminatives may afford some quick symptomatic relief and audible satisfaction, it must be remembered that flatulent dyspepsia is many times associated with disorders such as peptic ulcer, biliary tract disease, the irritable colon syndrome, alimentary tumours and ischemic heart disease.

METHYLPOLYSILOXANE (Simethicone, Dimethicone): This drug, a silicone derivative, is advocated in the symptomatic treatment of flatulence, bloating and distension. It is supposed to act as a defoaming agent, thus allowing easy escape of gases from the gastro-intestinal tract. However, though subjective relief is obtained, evidence to show that eructation is facilitated or that intestinal motility is improved is lacking. It is available as 40 mg. tablets.

APPETITE SUPPRESSANTS

Obesity is discouraged by the modern society for social as well as medical reasons. The incidence of diabetes mellitus, hypertension, angina pectoris and myocardial infarction is higher among obese individuals.

Except for certain endocrinal disturbances like Cushing's syndrome, the etiology of obesity is not well understood. No intrinsic metabolic or biochemical abnormality has been identified in obese persons. Recent work has shown that the fat cells of the obese are large (hypertrophic type of obesity) and that persons obese since childhood have a much larger number of fat cells than the lean persons (hyperplastic type of obesity). Although 'feeding' and 'satiety' centres have been identified in the hypothalami of animals, the role of the hypothalamus in the genesis of human obesity is not yet clear. Recent work suggests that the obese are basically less physically active than the slim ones. Many obese individuals show psychological disturbances and a compulsive desire to eat, though such individuals may not derive satisfaction from the act of eating.

In an obese individual, if an organic cause is present it should be treated appropriately. Obesity due to endocrinal disturbances falls in this category.

Commonly, obesity is due to excessive eating and lack of adequate exercise and not due to 'glands'. The patient must be made to appreciate this at the beginning of the treatment and must be explained clearly that diet is the mainstay of the treatment of obesity. For successful result, the patient must be adequately motivated by the concept of 'positive health'. It must also be emphasized that dietary treatment of obesity really consists of a lifelong reorientation of his eating habits (and often those of his family) and not merely of a 'course' of dieting. Individuals who look upon dieting as a course of treatment are bound to regain the lost weight and ultimately resign themselves to a crippled life of obesity. There are as many diets for obesity as there are physicians and like other fashions, each diet has had its vogue. It has, however, been convincingly shown that in the long run nothing about the diet matters except its caloric content. Hence, the best diet is one which is low in calorie content (1000-1500 per day), contains all the essential nutrients, provides a variety and is simple for the patient to follow for prolonged periods. It should also conform to the patient's pocket. Proprietary slimming foods are expensive and are an insult to the patient's intelligence as most patients seem to believe that they can lose weight by consuming them in addition to their normal diet. Prolonged fasting is a drastic measure, to be used rarely, only in resistant cases and that too under close medical supervision. The age-old Indian religious custom of fasting on certain days of the month has, however, much to recommend it, as it can atone for the minor sins of the palate indulged in at other times and thus, help to keep good health. If the patient realises the importance of dieting and exercise and if he has the necessary will, then in most of the cases the treatment of obesity is not difficult and can easily be carried out at home without the help of 'obesity clinics'. The results of therapy are likely to be more satisfactory in the hypertrophic than in the hyperplastic type of obesity. The patient should be told at the onset of therapy that an average weekly loss of only 0.5 kg. is excellent and would result in annual loss of about 26 kg.

Sometimes, even with the best of motivation, drastic reduction in the customary food intake is initially a trying experience. In such cases, appetite suppressants (anorexiants) may help the patient to adjust himself to his prescribed diet. It must be emphasized, however, that these drugs only supplement and are not a substitute for the dietary restrictions; in fact, by themselves they are valueless in the therapy of obesity nor can they be recommended for prolonged use.

Anorexiants, can be classified into:

- I. Amphetamine and related compounds.
- II. Bulk anorexiants.
- III. Miscellaneous drugs.

I. **Amphetamine and related compounds:** These are discussed in Chapter 14. Although their anorexiant effect appears to be related to the stimulation of the hypothalamus, the exact mechanism of appetite suppression by these drugs is not known. These drugs may cause excitement, agitation, insomnia and sometimes psychotic reactions with hallucinations. Their major drawback is the development of tolerance to the anorexiant effect and later, drug dependence. Withdrawal of these compounds after prolonged medication may cause drowsiness, sleep, tremors, fatigue and muscular weakness. These drugs are contraindicated in the presence of hypertension, hyperthyroidism and cardiovascular diseases.

The racemic form of amphetamine, because of its pronounced cardiovascular actions, is no more recommended in the treatment of obesity. The compounds employed are:

(i) **Dextroamphetamine sulphate** (Dexedrine): Which has predominant central and weak peripheral actions. Dose: 2.5 to 5 mg. The drug should be administered only during the day, the last dose being given before 6 p.m. The drug, however, has been extensively abused and should not be prescribed.

(ii) **Fenfluramine** (Ponderax): This analogue of amphetamine is claimed to have no central nervous system stimulant action. Further, it has been claimed to possess various metabolic actions in addition to its anorectic action. It appears unlikely that the metabolic actions as distinct from the anorectic effect contribute to the weight loss induced by this drug. It is available as 20 mg. tablets. It is used in the dose of 20-100 mg. daily. Double blind studies have shown similar weight losses and similar drop-out rates with this drug and with dexamphetamine. With restriction of diet, weight loss is slow and tolerance can develop. Adverse effects, though mild, can develop and include drowsiness, diarrhoea, dry mouth, insomnia, dizziness and headache. Although the drug does not cause central stimulation, mental depression following stoppage of fenfluramine therapy has been reported.

(iii) **Other compounds:** These do not offer any remarkable advantage over the compounds mentioned previously. Examples are phenteramine resin and phenteramine hydrochloride; phendimetrazine, diethylpropion, benzamphetamine, mazindol and chlorphenteramine hydrochloride. Mazindol is chemically unrelated to amphetamine.

II. **Bulk anorexiants:** Methylcellulose is non-digestible. When ingested, it swells and adds to the bulk in the diet. Though it is used as an appetite satiator in the treatment of obesity, it has proved no more effective than the high residue low caloric diet for the obvious reason, that an obese person is interested in eating good food and not something that would merely distend the stomach. Methylcellulose forms an important cheap constituent of many 'costly' commercial preparations advertised for the treatment of obesity.

III. **Miscellaneous drugs:**

Thyroid and related materials: Though frequently used in the treatment of obesity thyroid medication is not useful except to correct any associated thyroid deficiency. This is so because the doses of thyroxine required to raise metabolic rate sufficiently produce intolerable side effects.

Biguanides: Biguanides have been reported to induce weight loss in some non-diabetic obese individuals. This effect may be due to their anorectic effect, a reduction in gastrointestinal carbohydrate absorption, and a marked reduction in fasting and post-prandial hyperinsulinism which so often accompanies obesity. They are especially worth trying in patients with a family history of diabetes mellitus. They are discussed in detail in Chapter 59.

DRUGS FOR PREVENTION AND TREATMENT OF ATHEROSCLEROSIS

Atherosclerosis, a disease which affects the blood vessels, is now a leading cause of death in many developed countries. It is defined by W.H.O. Committee as "a variable combination of changes of the intima of arteries (as distinct from arterioles) consisting of focal accumulation of lipids, complex carbohydrates, blood and blood products, fibrous tissue and calcium deposits, and associated with medial changes." This results in a narrowing of blood vessels such as cerebral and coronary arteries.

A number of factors have been blamed

in the pathogenesis of atherosclerosis. Thus, in the words of Dr. Howard, "The person least likely to get atherosclerosis is a hypotensive, bicycling, unemployed, hypobetalipoproteinic, premenopausal female dwarf, living in a crowded room on the island of Crete before 1925 and subsisting on a diet of uncoated cereals, safflower oil and water." A lot of experimental and epidemiological evidence suggests a relationship between atherosclerosis and elevated levels of plasma lipids (cholesterol and triglycerides). Thus, it is known for long that rabbits fed on cholesterol develop fatty arterial lesions; the cholesterol present in the vessel wall probably comes from the plasma. Although there is no diagnostic abnormal pattern of the plasma lipids in subjects with atherosclerosis, an increase in plasma triglycerides and cholesterol has been observed in such patients. The incidence of ischaemic heart disease has been demonstrated to be higher among individuals with high plasma cholesterol and triglyceride levels than those with low levels. Conversely, the risk of ischemic heart disease in individuals with hypercholesterolaemia is about thrice as great as in those with normal plasma cholesterol levels. It has been suggested, therefore, that a reduction of plasma lipid levels either by dietetic restriction or by drugs may prevent the development of atherosclerosis or arrest its progress. It must be pointed out, however, that there is yet no direct evidence showing that lowering of plasma lipid levels does in fact exert such beneficial effects. Recent evidence indicates that reduction of plasma lipids does not affect the prognosis once the myocardiac infarction has occurred.

Being insoluble in water, the plasma lipids are present either as (a) microglobules called chylomicrons, or as (b) lipoproteins, in combination with proteins. There are three classes of lipoproteins in the plasma: very low density lipoproteins (VLDL), low density lipoproteins (LDL), and high density lipoproteins (HDL). The lipid in the chylomicrons and VLDL is mostly triglycerides whereas that in the LDL is mostly cholesterol. The normal fasting plasma is clear and contains about 700 mg. of total lipids, made up of almost equal proportions of triglycerides, phospholipids and cholesterol. About 70 per cent of cholesterol is in ester form. The plasma shows opalescence or lactescence due to chylomicrons after ingestion of a fatty meal. This lipemia is rapidly cleared by a heparin-activated lipoprotein lipase called 'clearing factor'.

Hyperlipoproteinemias which are incriminated in the pathogenesis of atherosclerosis may be due to hypercholesterolemia and/or hypertriglyceridemia and may be divided into (a) the rarer primary varieties, Type I to Type V: These are hereditary, occur in younger subjects and all (except Type I) lead to premature development of atherosclerosis. Type I is associated with ingestion of fats. Type II is unrelated to dietary factors. Type III to V are carbohydrate induced and associated with insulin resistance as well; and (b) the much commoner secondary varieties due to dietary, racial and hormonal factors, and occurring in association with hypothyroidism, diabetes mellitus, alcoholism, nephrotic syndrome and a variety of other diseases.

In the management of hyperlipoproteinemia, weight reduction, appropriate modification of diet, abstinence from alcohol and specific treatment of the causative disease, if any, such as hypothyroidism and diabetes mellitus, is much more important than therapy with drugs used to lower plasma lipids.

The cheapest and the most reliable method for lowering the plasma lipids is the intake of a diet containing a higher proportion of polyunsaturated fats such as groundnut oil, sunflower oil, safflower oil or cotton seed oil instead of saturated fats. Simultaneous restriction of total caloric intake and of saturated fats like animal fats and hydrogenated oils is recommended. To this formidable list, a reduction in the dietary intake of sucrose may now be added. In those patients in whom these measures are not successful in lowering the elevated plasma lipids and in those who find the dietary restrictions irksome, drug therapy should be used with the understanding that it will have to be continued life-long. This is so because the drugs do not cure the basic disorder of lipoprotein metabolism but symptomatically control only one aspect of the disease process.

It must be emphasized that, in general, the results of drug treatment of atherosclerosis are so far disappointing. There is no single drug which can be used safely over a prolonged period to reduce the various blood lipids, as desired.

Drugs used to lower plasma lipids may act predominantly (1) on elevated triglyceride levels (clofibrate, nicotinic acid and heparin), or (2) on elevated plasma cholesterol levels (Cholestyramine, thyroid hormones and estrogens).

(1) CLOFIBRATE (Atromid S, Lolipid): This drug, ethyl-chlorphenoxy isobutyric acid, lowers elevated plasma levels of phospholipids, cholesterol and triglycerides, in appropriate cases. The triglycerides levels show the maximum response. It has also been claimed to reduce plasma fibrinogen level, to increase fibrinolysis and to reduce abnormal platelet stickiness.

Mechanism of action: The exact mechanism of action is not clear but it is believed to act by inhibiting the hepatic synthesis of cholesterol and the transfer of triglycerides from the liver to the plasma.

Absorption, fate and excretion: Clofibrate is well absorbed from the gut and exists in the plasma as chlorphenoxyisobutyric acid bound to albumin. It has a plasma half life of about 12 hours and appears in the urine as the glucuronide.

Adverse reactions: This drug occasionally produces allergy, nausea or diarrhoea. It increases the body weight in about 50 per cent of the patients, probably due to fluid retention. It displaces acidic drugs such as coumarin anticoagulants and tolbutamide from the binding sites on plasma proteins. Hence, the dosage of these drugs should be reduced during clofibrate therapy. Serum transaminase levels sometimes show a rise. Though rare, potentially serious effects on skeletal and cardiac muscle have been reported. Long-term therapy is associated with an increase in gallstone formation.

Therapeutic uses: Clofibrate (1.5-2.0 g. daily) has been most extensively studied in patients with ischemic heart disease. British experience suggests that in the treatment of ischemic heart disease, clofibrate is likely to reduce the occurrence of infarction and sudden death in patients who suffer from angina but have not had a myocardial infarct. Such benefit was not seen in patients who had already had an infarct by the time clofibrate was started. The beneficial effect of clofibrate did not necessarily correlate with its action in lowering the plasma lipids. Routine use of clofibrate in all patients who have ischemic heart disease but who do not even have angina has been advocated by some workers. On the other hand, the American Coronary Drug Project has failed to confirm any reduction in the mortality in patients with ischemic heart disease treated with either clofibrate or with nicotinic acid.

The drug is also used frequently for prevention and treatment of atherosclerotic arterial disease, though its usefulness is not well established. It may be noted that even in cases of angina, the beneficial effects of clofibrate were not related to its effects on serum lipids.

The drug has also been used to reduce plasma lipids in patients with diabetic retinopathy and xanthomas, with some success.

(2) NICOTINIC ACID: This vitamin, when administered orally in a large dose of 3 to 6 g. (50 times the daily requirement), produces a fall in the plasma triglyceride and to a much smaller extent in plasma cholesterol levels. The related compound nicotinamide does not possess

such a hypocholesterolaemic effect.

The major drawbacks of nicotinic acid are development of flushing, pruritus, nausea, vomiting and colicky pain, seen in as many as 25 per cent of the patients. Large doses over a long period may cause disturbances in liver functions, elevation of serum uric acid levels and reduction in glucose tolerance. Nicotinic acid is also used as a vasodilator.

(3) HEPARIN: Heparin reduces the elevated levels of plasma triglycerides by releasing a tissue lipase, lipoprotein lipase, into the circulation. This action is transient and frequent injections are required to produce a sustained effect. This makes the plasma lipid lowering action of heparin one of theoretical interest.

(4) CHOLESTYRAMINE RESIN: Cholestyramine resin, an insoluble chloride salt of a basic anion exchange resin has a strong affinity for bile salts (cholates) in the intestine. It binds the cholates into an insoluble complex which is excreted in faeces. Prevention of cholate reabsorption leads to a marked increase in their synthesis from plasma cholesterol and a consequent reduction in serum cholesterol levels. The drug, however, does not significantly lower the plasma levels of phospholipid and triglyceride. It is administered by mouth in the dose of 15 g. per day. The adverse effects include nausea, vomiting and constipation. Doses over 30 g. per day may interfere with absorption of fats and fat-soluble vitamins, causing steatorrhoea. It also interferes with the absorption of ingested thyroid hormones and organic acids such as chlorothiazide, phenylbutazone, phenobarbitone and tetracycline. Cholestyramine resin may be useful in relieving pruritus associated with biliary cirrhosis and cholestatic jaundice.

Colestipol, like cholestyramine, is a bile acid sequestrant. It is used in dose of 4-5 g. thrice daily.

(5) SODIUM DEXTROTHYROXINE: Elevated serum cholesterol levels are often observed in patients with myxedema, while hyperthyroid individuals show reduced serum cholesterol levels. The laevorotatory form of thyroxine, though effective in lowering serum cholesterol, produces a marked increase in the oxygen consumption and manifestations of hyperthyroidism; the dextro form, although less potent in lowering serum cholesterol, has lower metabolic activity and hence, has been employed as a hypocholesterolaemic agent. Its effect on triglycerides is insignificant.

Most of the available evidence indicates that dextrothyroxine increases the turnover of cholesterol and promotes the excretion of cholesterol and its degradation products in the faeces via the biliary route.

The adverse effects include development of angina pectoris, palpitation, tremor, insomnia, hyperthermia and diarrhoea. The compound potentiates the effects of coumarin anticoagulants. The drug is contraindicated in individuals with cardiac damage, hypertension and advanced liver or kidney disease.

Initially, the drug is given in the dose of 1 to 2 mg. daily. It is increased by 1 or 2 mg. at monthly intervals till a dose level of 6 to 8 mg. per day is reached.

(6) ESTROGENS: These can reduce the plasma cholesterol and beta lipoprotein cholesterol but elevate the plasma triglyceride levels. However, the amount needed to achieve this effect often produces gynaecomastia and decreased libido in males and hence, they are of little practical value. Besides, a high incidence of occlusive vascular complications has recently been demonstrated during treatment of prostatic carcinoma with diethyl stilbesterol.

(7) PROBUCOL: This newer cholesterol lowering agent is variably absorbed orally. It is slowly metabolized and excreted over a period of months. Its mechanism of action is not known. The drug is under evaluation.

36 Emetics, Drug Therapy of Vomiting and Diarrhoea

The faculty of vomiting is present in most mammals except rodents, a species that lacks the vomiting centre. Some animal species like the herbivora do not vomit.

Physiology of vomiting: The act of vomiting is accompanied by a complex of movements which are controlled by the vomiting centre present in the dorsal portion of the lateral reticular formation. The afferent and the efferent pathways which bring about vomiting are carried both by vagus and sympathetic nerves. A major sensory relay station in the afferent vomiting pathway is the chemoreceptor trigger zone (CTZ), situated in the lateral border of the area posterema of the medulla oblongata. A variety of agents including drugs like morphine, apomorphine, alkylating agents and digitalis glycosides stimulate the CTZ while the phenothiazines and certain antihistaminics depress it. It must be pointed out, however, that the CTZ being a purely sensory relay station is incapable of initiating vomiting in the absence of vomiting centre, while direct electrical or chemical stimulation of the latter can evoke vomiting irrespective of the CTZ. Vomiting is usually preceded by the sensation of nausea and increased secretion of saliva, bronchial fluid and sweat. The muscles involved in the act of coughing take part in the act of vomiting, and the vomiting, vagal and cough centres have a close functional relationship. Vomiting is partially under the volitional control and can be induced voluntarily, more easily by children than by adults.

Emetics: The drugs that produce vomiting are termed emetics. These can be classified according to their site of action as:

I. Centrally acting by stimulation of the CTZ e.g. apomorphine, morphine and hydergine.

II. Peripherally acting e.g. mustard, copper sulphate, antimony and potassium tartrate (tartar emetic) and hypertonic sodium chloride.

III. Both peripherally and centrally acting e.g. ipecacuanha and digitalis glycosides.

I. Centrally acting emetics:

APOMORPHINE: This drug is described in Chapter 8. On subcutaneous administration of the drug in the therapeutic dose, vomiting is produced within 15 minutes. In hypersensitive individuals, however, even a subtherapeutic dose may elicit severe emesis and collapse. Vomiting is less severe in a recumbent than in an erect subject and is often accompanied by sedation. Apomorphine-induced vomiting is effectively suppressed by chlorpromazine. Apomorphine in larger doses often produces restlessness, tremors, occasionally convulsions, and central respiratory depression. The drug sometimes may cause tachycardia, hypotension, syncope and coma. Any side effects can be treated by a specific antidote, nalorphine 5-10 mg. given intravenously.

Apomorphine injection I.P. contains 3 mg. of the salt per ml. with sodium metabisulphite as preservative. Dose: 2 to 8 mg. by subcutaneous or intramuscular injection.

Other centrally acting drugs, which cause vomiting as a side effect, are discussed elsewhere.

II. Peripherally acting emetics: These cause vomiting reflexly by irritation of the gastric mucosa; vomiting will not be induced if the vagi are cut. These drugs are:

MUSTARD: This acts by virtue of its volatile oil which is formed as a result of a reaction between a glycoside and an enzyme, in the presence of water. Although it is uncertain in action, it is safe and easily available. Hence, it forms one of the common household remedies. Dose : 1 teaspoonful in water.

SODIUM CHLORIDE (hypertonic): Given orally, it withdraws fluid from the cells lining the stomach and thus causes irritation which causes reflex emesis. Part of the salt penetrates the cells and produces salt action which may also be partly responsible; the more penetrating salts like ammonium chloride are more effective emetics than the less penetrating salts like sodium sulfate.

COPPER SULPHATE: Copper sulphate is a peripherally acting emetic which evokes vomiting by irritation of the gastrointestinal tract. Being a metal salt, it has an astringent action.

For evoking emesis, 300 mg. of copper sulphate, dissolved in 200 ml. of water are administered by mouth. Vomiting occurs within 10 to 15 minutes. Failure of vomiting to occur within this period necessitates a second dose to prevent the passage of the compound into the small intestine as it will cause colic and diarrhoea. If it fails to produce emesis, a stomach wash must be given, as it would act as a poison. It is now rarely used.

III. **Both peripherally and centrally acting emetics:** Though ipecacuanha and cardiac glycosides produce vomiting, their other pharmacological actions are overwhelmingly more important and hence, they are discussed elsewhere. Digitalis is too toxic to be employed as an emetic but ipecacuanha syrup is a much safer emetic than apomorphine. It can be administered safely in children. Furthermore, the drug can evoke emesis in poisoning with drugs that depress the CTZ e.g. chlorpromazine. The usual adult dose is 15 ml. by mouth which may be repeated after 20 minutes if the individual fails to vomit. The drug should not be used as an emetic in unconscious patients and in those poisoned with caustics, corrosives, petroleum products or strychnine.

Therapeutic uses of emetics: The use of emetics in therapeutics is limited to certain cases of poisoning especially where facilities for gastric lavage are not available. This is because aspiration of the gastric contents into the respiratory passage may occur during emesis. Further, if the ingested poison is a caustic, emesis may cause perforation of the stomach. The central depressant action of emetics like apomorphine may sometimes make the patient's condition worse and severe emesis can cause collapse and even death. Emetics should be administered with caution in children and the elderly, in pregnant women and in subjects with cardiac decompensation, hypertension, hernia, peptic ulcer and pulmonary tuberculosis.

DRUG THERAPY OF VOMITING

Physiologically, vomiting acts as a protective mechanism and helps to expel undesirable material from the stomach. In many situations, however, nausea and vomiting seem to serve no discernibly useful function. In this context it must also be appreciated that similar stimuli in progressively increasing intensity may produce successively anorexia, nausea and vomiting.

There appear to be wide differences in individual susceptibility to 'become sick' e.g. infants are less susceptible to motion sickness than older children and adults (among whom again there are wide individual differences); women are more susceptible than men and the aged are less susceptible than the young adults to postanaesthetic vomiting. Estrogens are believed to lower the threshold of the CTZ, thus possibly explaining the vomiting of pregnancy and the nausea during oral contraceptive therapy.

Vomiting may be psychological in origin and initiated by sights, smells or certain associations. Secondly, it may arise reflexly from the G.I. tract, the impulses being conveyed (probably directly to the vomiting centre) by both the vagus and the sympathetic nerves. Thirdly, impulses arising from the vestibular apparatus are the primary cause of motion sickness though sight of others vomiting, odours associated with the ship and the expectation of vomiting may all contribute to it. Fourthly, drugs (apomorphine, morphine, ergot derivatives, digitalis glycosides, nitrogen mustards) and many metabolites (as in uremia) may act on the medullary centres to produce vomiting. Finally, any pain, if sufficiently severe, may make a person 'sick' and vomit.

The treatment of vomiting consists of:

I. Treatment of the cause e.g. relief of pain, removal of intestinal obstruction, treatment of colic by antispasmodic drugs, reduction in the intracranial tension or correction of metabolic acidosis.

II. Symptomatic treatment using antiemetic drugs to stop vomiting. Antiemetics must never be used without establishing the cause of vomiting, as they may mask an underlying disease and so delay the diagnosis.

III. Supportive therapy e.g. correction of dehydration and associated electrolyte disturbances.

Antiemetic agents are drugs used specifically to prevent or relieve nausea and vomiting. They include chlorbutanol, phenobarbitone, hyoscine, certain antihistamines, phenothiazines and metoclopramide. They are all centrally acting drugs with a sedative action. In addition they also act at:

(1) The vomiting centre—anticholinergics or antihistamines e.g. dimenhydrinate, cyclizine;

(2) The CTZ in the fourth ventricle—phenothiazines e.g. chlorpromazine, prochlorperazine;

(3) The periphery—e.g. anticholinergics and metoclopramide, which increases rate of gastric emptying.

CHLOROBUTANOL (Chloretone): This compound, structurally related to chloral hydrate, has a hypnotic action and a mild local anaesthetic activity. It may, therefore, act both locally and centrally to relieve vomiting, particularly in acute gastroenteritis. Chlorobutanol occurs as colourless crystals with a slightly astringent taste. It is now mainly used as a local analgesic in dusting powders and toothache drops, and as a preservative for adrenaline and posterior pituitary solutions. The oral antiemetic dose is 300 to 1000 mg.

Phenobarbitone acts by its sedative action. Hyoscine blocks the afferent impulses to the vomiting centre by its anticholinergic action; its mild sedative action also contributes to its antiemetic effect. It is the drug of choice in motion sickness. Certain antihistaminic drugs (dimenhydrinate, cyclizine, promethazine and meclizine) act as antiemetics by their action on the vomiting centre and by their mild sedative effect. They are effective in motion sickness and in vomiting due to labyrinthine disorders (vestibular neuronitis, Meniere's disease etc.). Phenothiazines selectively depress the CTZ but have no action on the vomiting centre. Hence, they are ineffective in motion sickness. They are, however, the drugs of choice in nausea and vomiting due to uremia, carcinomatosis, radiation sickness and that due to drugs (morphine, tetracyclines, chloroquine, antimetabolites, alkylating agents). In general, the phenothiazines are preferred when vomiting is severe and potentially hazardous but is likely to be of short duration e.g. postoperative vomiting. On the other hand, the antihistaminic antiemetics are safer, though less effective, than the phenothiazines and are generally preferred for long term use e.g. in vomiting of pregnancy, malignancy and that due to antimalignancy compounds.

Among the phenothiazines, triflupromazine and the piperazine phenothiazines are more effective than others. However, their extrapyramidal adverse effects must be remembered. Vomiting due to gastroenteritis does not respond well to antiemetic drugs. Cyclizine may, however, be tried in nausea due to hepatitis.

METOCLOPRAMIDE (Mexolon, Perinorm): This antiemetic is chemically related to procainamide. Its antiemetic action is central as it prevents the vomiting induced by centrally acting emetic, apomorphine. It probably acts by blocking the central dopaminergic receptors. Its effects on the gut, however, appear to be peripheral in origin.

Pharmacological actions: The drug increases the resting tone of the gastroesophageal sphincter and stimulates the co-ordinated gastric movements to speed up gastric emptying. An injection of 20 mg produces gastric emptying within 90 minutes in most patients. It also increases pyloric activity and duodenal peristalsis and accelerates the transit along the small bowel. It has probably no action on the biliary tract. Its actions on the G.I. tract are antagonized by anti-cholinergic drugs. Metoclopramide reduces post-operative vomiting, vomiting due to morphine and pethidine, vomiting of labyrinthine origin but is ineffective in vomiting due to cancer chemotherapeutic agents.

The drug stimulates the secretion of prolactin.

Adverse reactions: It may occasionally produce extrapyramidal effects. Other adverse reactions include diarrhoea, lassitude, skin rash, lactation and gynecomastia.

Preparations and dosage: It is available as 10 mg tablets, as syrup, and as an injection. The oral dose is 5-10 mg thrice daily, the total daily dose not exceeding 0.5 mg/kg body weight.

Therapeutic uses: It is used (1) as an antiemetic especially in the post-operative state, (2) to prevent vomiting during induction of anaesthesia and to accelerate the gastric emptying in order to prepare patients for general anaesthesia for emergency surgery, and (3) to treat gastric retention, following gastric surgery.

The drug has also been claimed to help patients with gastritis, reflux esophagitis, hiatus hernia, persistent hiccup and functional dyspepsia. These claims need further confirmation.

Therapy of vomiting of pregnancy: The exact etiology of vomiting of early pregnancy is not established and the treatment, therefore, is purely empirical.

The patient is advised to take more fluids and sweets. Psychotherapy including reassurance and placebo therapy are often beneficial. Though it is ideal to avoid all drugs in the first trimester, some women are severely nauseated and need drug therapy. Drugs usually employed are vitamin B_6 (pyridoxine) antiemetic antihistaminics, and phenothiazines. The relative usefulness of pyridoxine as an antiemetic and its mechanism of action are not known. Phenothiazines are discussed in Chapter 11. Finally, vomiting due to an unrelated condition such as peptic ulcer, hepatitis, drug reaction or gall bladder disease should not be forgotten.

Therapy of motion sickness: Motion sickness is a recognized clinical entity for over 2000 years and has been mentioned by Hippocrates. It is a syndrome characterised by vertigo and nausea resulting from body motion. The word 'nausea' is derived from Greek word 'nautical' as it usually occurs on the sea. It is estimated that approximately 50 per cent of individuals undertaking sea travel suffer from this disturbance.

It has been established that the receptors for motion sickness are in the vestibular apparatus. Bilateral labyrinthectomy or sectioning of the 8th cranial nerve in animals prevents motion sickness. As with many complex reflexes, other stimuli such as visual, proprioceptive and emotional, may facilitate or enhance motion sickness. As a rule, children are more susceptible to motion sickness and the vulnerability diminishes with advancing age. Deaf persons with disease of the inner ear and infants, however, do not get motion sickness.

Drugs that block acetylcholine in the central nervous system e.g. scopolamine and those which activate the central sympathetic areas e.g. d-amphetamine have been shown to be highly effective in the treatment of motion sickness. The drugs used are:

(i) SCOPOLAMINE AND ATROPINE: The belladonna alkaloids, particularly scopolamine (Hyoscine), were among the first drugs to be used in the treatment of motion sickness. Scopolamine 0.6 mg. has been demonstrated to be superior to all other anti-motion sickness drugs. A remarkable advantage of hyoscine is its ability to confer protection from motion sickness without producing significant drowsiness.

Scopolamine is much more effective when employed prophylactically than during an attack. A single dose of 0.3 to 0.6 mg. by mouth in an adult, 15 minutes before food and 30 minutes before journey, gives satisfactory protection. The onset of the antiemetic effect usually coincides with the development of dryness of mouth. The drug action persists for 2 to 3 hours and in the event of a prolonged journey, an additional dose of 0.1 to 0.2 mg. may be administered after 2 hours.

The mechanism of protection conferred by this agent is not known. A central antagonism of acetylcholine or related substances may be the basis of its therapeutic efficacy. Given alone, the drug may sometimes cause drowsiness, dizziness, blurring of vision, dryness of mouth and urinary retention.

(ii) d-AMPHETAMINE in the dose of 10 mg. is also highly effective. Combination of scopolamine 0.6 mg. and d-amphetamine 10 mg. is synergistic in action and is most effective in motion sickness. It also counters drowsiness due to scopolamine. An equally effective combination is that of promethazine (Phenergan) 25 mg. with d-amphetamine 10 mg.

(iii) ANTIHISTAMINICS: A number of antihistaminic agents have been employed in the treatment of motion sickness. These include the phenothiazine antihistaminics promethazine and its chlorotheophyllinate, dimenhydramine, and the piperazine antihistaminics cyclizine, meclizine and cinnarizine. These are discussed in Chapter 20. Carefully controlled studies in humans, however, indicate that all these drugs are less effective than the scopolamine-d-amphetamine combination.

The number of individuals protected from motion sickness by these agents varies from 60 to 70 per cent. The drugs are administered by mouth, 30 minutes before undertaking the journey. The piperazine antihistaminics have a more prolonged action than the other compounds, a single dose providing relief for 12 to 24 hours or more.

DRUG THERAPY OF DIARRHOEA

Diarrhoea is a very common problem in the tropical and subtropical countries and like vomiting, can be caused by a variety of conditions varying from infections and allergy to emotional disturbances. It is defined as the frequent passage of liquid faeces with or without blood or mucus; in the case of former it is usually due to a known cause such as amoebic or bacillary dysentery.

The treatment of diarrhoea consists of:

I. **Specific treatment** of the cause such as using specific antibacterial, anthelmintic or antiprotozoal agents. These are discussed in detail elsewhere. Specific therapy of diarrhoea is easy, if the pathogen responsible can be detected. This, however, is not practicable in routine practice and one has to depend on clinical judgement. Although classical cases such as those due to amoebic or bacillary dysentery can easily be diagnosed clinically, in vast majority of cases with diarrhoea, no pathogens may be detected. Such a diarrhoea with 'negative stool' could be due to the presence of Staphylococcal exotoxin, E. coli, endotoxin, viruses or other unknown agents. Wherever possible, stool culture is advisable, particularly in chronic diarrhoeas. Reckless use of broad spectrum antibiotics routinely in all diarrhoeas, particularly repeated and over a prolonged period, when there may not be any pathogen to kill, is wasteful and very hazardous.

Some of the diarrhoeas associated with fat malabsorption improve following substitution of medium chain triglycerides in place of long chain fatty acids. Similarly, osmotic diarrhoea due to intestinal disaccharidases deficiency can improve on dietetic reduction of milk and dairy products which contain lactose. Diarrhoea due to carcinoid syndrome responds to 5-HT antagonists while that due to blind loop syndrome responds to proper anti-bacterial therapy.

II. **Symptomatic and supportive therapy** includes control of diarrhoea with anti-diarrhoea agents and correction of dehydration and electrolyte disturbances. *The latter is the most important aspect of treatment of severe diarrhoea.* Drugs used in the symptomatic treatment of diarrhoea can be divided into:

(1) Gastrointestinal protectives and adsorbents.

(2) Drugs affecting gastrointestinal motility.

(3) Miscellaneous agents.

(1) **Gastrointestinal protectives and adsorbents:** These agents are mainly useful by virtue of their ability to adsorb noxious substances such as gases, bacteria and bacterial toxins. In addition, some of these possess an astringent action while others protect the gastrointestinal mucous membrane from the irritants by coating it mechanically. They are, as a rule, cheap and devoid of adverse effects but their usefulness is restricted mainly to the treatment of mild and infrequent episodes of diarrohoea. The commonly employed substances of this class are:

BISMUTH SALTS: The routinely employed bismuth salts are bismuth subcarbonate and bismuth subgallate.

The bismuth salts have an astringent, protective and adsorbent effect. Given orally, they are devoid of serious toxic manifestations. They are expensive.

Bismuth subcarbonate I.P. and bismuth subgallate I.P. are insoluble in water and are administered by mouth as constituents of a binding mixture; the dose of subcarbonate being 0.6 to 2 g. while that of subgallate is 1 g.

PREPARED CHALK (Creta preparata), a native form of calcium carbonate containing not less than 97 per cent of calcium carbonate, is often used as an antacid as well as in the treatment of diarrhoea. In diarrhoea, it probably acts as a protective by covering the intestinal mucous membrane. It is generally given in the dose of 1 g. in the form of suspension. Aromatic powder of chalk contains, in addition, aromatic ingredients like cinnamon, clove, cardamom seeds and sucrose. It is used as an antacid and a carminative. The drug is quite cheap.

LIGHT KAOLIN is a hydrated aluminium silicate (clay) purified and free from gritty particles. When employed in the treatment of diarrhoea, it is believed to act as an adsorbent of bacteria and bacterial toxins.

Light kaolin I.P. is a light, white, odourless and tasteless powder practically insoluble in water. It is recommended orally in the dose of 15 to 60 g. at 6 hourly intervals, as thick, flavoured suspension, for 5 to 10 days. However, patients usually do not like to take more than 4 g. at a time. A mixture containing 20 per cent kaolin with 1 per cent pectin, in a sweetened and flavoured tragacanth suspension, is recommended orally in the dose of 30 ml. in the treatment of abnormal intestinal fermentation.

PECTIN: It is a purified carbohydrate product obtained from the dilute extract of the inner portion of citrus fruits or from apple pomace. It consists chiefly of partially methoxylated polygalacturonic acids.

The mechanism of antidiarrhoeal effect of pectin is not clear. When ingested, it passes into the intestinal tract where it probably acts by mechanical coating. It helps to produce formed stools. It is decomposed in the colon by bacterial action.

Pectin I.P. occurs as a coarse or fine yellowish white, odourless, tasteless powder which forms a viscous, opalescent, colloidal solution with 20 parts of water. The solution is acidic in character. It may be administered either as a colloidal solution alone or with kaolin, or in the form of apple pulp.

ACTIVATED WOOD CHARCOAL: This preparation is the residue from the destructive distillation of vegetable matter such as saw dust, cellulose residue and coconut shells, treated with zinc chloride to increase its adsorptive power. It is widely employed in the treatment of flatulence, dyspepsia and various types of diarrhoeas, as a suspension in water for gastric lavage and for the emergency treatment of poisoning with alkaloids like morphine, strychnine and atropine. Activated wood charcoal I.P. is a fine, black, odourless, tasteless powder free from grit. It is usually administered by mouth in the dose of 4 to 8 g. or as a constituent of *Universal Antidote* containing 2 parts of charcoal with 1 part each of magnesium oxide and tannic acid in the treatment of alkaloidal poisoning. The home-made Universal Antidote consists of burnt toast 2 parts, strong tea 1 part and milk of magnesia or chalk (calcium carbonate) 1 part.

It may be noted that chalk, kaolin and charcoal can interfere with the absorption of antibiotics.

MAGNESIUM TRISILICATE, in addition to being an effective antacid, also has adsorbent properties. It reacts with gastric hydrochloric acid to form gelatinous silicon dioxide which protects the mucous membrane. It is administered by mouth in the dose of 1 g. 4 times a day.

(2) **Drugs affecting gastrointestinal motility:** The opiates are powerful and reliable inhibitors of propulsive activity of the bowel. Hence, they are useful in the treatment of severe diarrhoea. However, tincture of opium can be dangerous in infants and small children. The drugs used are: (i) codeine, in the dose of 30 to 60 mg. at 4 to 8 hourly intervals, (ii) camphorated tincture of opium in the dose of 4 to 8 ml. every 6 to 8 hours and (iii) diphenoxylate, a pethidine substitute with a low addiction liability, in the dose of 5 mg. along with 0.25 mg. of atropine (Lomotil) 3 to 4 times a day. Loperamide is a new antidiarrhoeal agent which is believed to act directly on intestinal muscle.

The belladonna alkaloids, particularly atropine and its synthetic substitutes such as propantheline, are often useful to relieve colic associated with diarrhoea. They are particularly useful in controlling "intestinal hurry" following gastrectomy and certain drugs like guanethidine. Their use in chronic diarrhoeas, however, is not without danger and they may precipitate paralytic ileus in patients with regional enteritis and fulminating ulcerative colitis. The commonly employed preparations are atropine sulphate 0.25 to 1 mg., or belladonna tincture 0.6 to 2 ml. New atropine substitutes do not offer any significant advantage over atropine.

(3) **The miscellaneous drugs:**

ASTRINGENTS: The astringents, because of their ability to precipitate superficial proteins, form a layer on the mucous membrane and protect it from irritation. Bismuth salts are commonly used for this purpose. The tincture of black catechu, when administered by mouth, releases tannic acid in the small intestine and is sometimes used in the dose of 4 to 6 ml. Pure tannic acid is decomposed into gallic acid by the gastric juice and hence, is not useful.

LACTOBACILLUS ACIDOPHILUS: This preparation, available in the form of tablets, is administered by mouth to favour the growth of normal intestinal flora in the treatment of certain chronic diarrhoeas. Administration of butter milk or curds would probably serve a similar purpose.

BERBERINE: Berberine, an alkaloid obtained from the plant *Berberis arista* has been claimed to be effective in the treatment of diarrhoea. It is administered orally in the dose of 150 mg. thrice daily. The mechanism of action is not known. The drug has been shown to inhibit the cholera-toxin induced inflammation in rats and is claimed to be useful in the treatment of cholera.

Other drugs used in the treatment of diarrhoeas include the 5-HT antagonist cyproheptadine employed in dumping syndrome, the glucocorticoids used in the treatment of ulcerative colitis and folic acid in the treatment of tropical sprue. These are discussed elsewhere.

37 Pharmacotherapy of Constipation

It appears that people have been very particular about the 'regular bowel habit' from the earliest times and purgation, believed to be the panacea for many diseases, formed an important part of medieval therapeutics. At one time it was almost fashionable to take a regular purge or an enema to keep the bowels clean. "Fashionable seventeenth-century France was a trend-setter. Louis XIII had 212 enemas, 215 purgations and 47 bleedings in one year. With Louis XIV, the enema came into its own. It became a household ritual and most upper-crust people had one every day. A celebrated legal case concerned payment for the administration of 2,190 enemas, all within two years to a Canon of Troyes." The fashion also spread to England and America and in the Victorian era constipation was treated with every conceivable concoction. Even today, many people have wrong notions about the quantity, consistency and frequency of stools in health and 'ritual purgation of children and the obsessional catharsis of adults' is still not uncommon. Cathartics are widely advertised for the treatment of constipation and are extensively used by lay people as they are easily available at the counter without a doctor's prescription. Almost half of the patients suffering from digestive tract disorders complain of 'Constipation' and many times drugs are self-prescribed without medical advice.

Drugs which are used to promote defaecation are called *cathartics.*

Experimental evaluation: Many methods have been evolved to study the secretory and the motor functions of the gastrointestinal tract. Thus, the secretory response in dogs can be studied by *in vivo* preparations like the fundic pouch of Heidenhain and the Pavlov pouch. The former is devoid of vagal innervation, while in the latter, the vagus nerve is intact. Chronic total gastric, biliary, pancreatic and intestinal fistulae have also been described in animals like cats and dogs, to study the secretory activity of these portions.

Secretory response of human stomach provoked by administration of agents like histamine, alcohol, insulin and pentagastrin, can be measured readily and is clinically employed for diagnosis.

The effect of drugs on the motility of the gastrointestinal tract can be studied by a variety of *in vitro* animal preparations like isolated guineapig ileum, rat fundal strip, rat colon and rabbit duodenum. Some of these, like rabbit duodenum, possess an inherent rhythmic contractile activity on which the drug action is superimposed, while other tissues like guineapig ileum are normally devoid of spontaneous activity but contract or relax on addition of a drug.

The *in vivo* methods of studying gastrointestinal motility in animals involve either direct visualisation through a surgically made transparent abdominal window, administration of barium meal or insertion of a balloon within an intestinal loop connected to a recording system. The parallel human methods include radiological examination after administration of barium meal and use of food markers like charcoal, colouring agents, beads and radioactive isotopes.

Physiology of defaecation: Intestinal movements are mainly of three types: pendular—due to annular contraction of longitudinal muscles, segmental—due to contraction of circular muscles and peristaltic. The first two are responsible for mixing of the food while peristalsis also helps in propulsion. Normally, food leaves the stomach in about ½ to 2½ hours and its residue reaches the caecum by about 5 to 6 hours. It takes approximately 18 to 24 hours before the process of evacuation starts and the total time necessary for complete clearance of the ingested material is approximately 5 to 6 days. After ingestion of barium sulfate, the barium shadow can be first seen in the caecum at about 4½ hours, in the descending colon at about 11 hours and in the pelvic colon at about 18 hours. Usually, the peristaltic waves occur frequently upto ileum while they are very irregular in case of transverse, descending and pelvic portion of the colon, except during the gastrocolic reflex.

The gastrointestinal tract is innervated by both adrenergic and cholinergic nerves. Stimulation of the sympathetic or adrenergic nerves usually produces an inhibitory effect on the intestinal movements resulting in relaxation of the gut and closure of the sphincters. Stimulation of the vagus and other cholinergic nerves increases the tone and peristaltic movements. Emotions are known to play an important part in the physiology of gastrointestinal secretions and movements.

Normally, most of the ingested water and fluids secreted by various gastrointestinal glands are reabsorbed and only about 100 ml. of fluid is excreted with the faecal matter. Most of the absorption takes place in the small intestine and caecum. Hence, a cathartic which acts mainly in the small intestine is likely to produce considerable loss of fluids, electrolytes and nutrients from the gut. Furthermore, the absorption of food is also interfered with. On the other hand, cathartics which act only on the colon produce relatively less fluid loss and do not interfere with the absorption of food. Absorption of water continues even in the colon and the contents which are normally fluid upto ascending colon become semisolid during their passage through transverse and descending colon and are then stored as faecal matter in pelvic colon. The act of defaecation is initiated by distension of the rectum. If this sensation is ignored repeatedly, it may lead to the development of constipation.

The rate of intestinal passage of food depends on the nature of the diet and its fluidity. The greater the indigestible residue and water content, the more rapidly it reaches the rectum and produces its distension. Diminished intake of both water and indigestible residue can lead to constipation. Further, constipation, though commonly due to a lax, atonic colon, may also be associated with a hypersegmenting, highpressure bowel.

Classification of cathartics: These drugs are sometimes classified according to the intensity of action as mild (laxative), moderate or drastic. Laxative effect suggests the elimination of soft, formed stool without griping and without much loss of water. More commonly they are classified according to their mechanism of action.

I. **Stimulant or irritant cathartics:**

(a) Anthraquinone group e.g. cascara sagrada, senna, rhubarb and aloe.

(b) Irritant oils e.g. castor oil.

(c) Resinous compounds e.g. jalap and colocynth.

(d) Miscellaneous e.g. phenolphthalein, bisacodyl.

Depending on the dosage, all these drugs cause variable amount of griping, mucus production and fluid loss.

II. **Osmotic cathartics e.g.** magnesium sulfate, milk of magnesia, magnesium citrate, potassium sodium tartrate and lactulose.

III. **Bulk laxatives** e.g. methyl cellulose, agar agar, plantago seeds and bran.

IV. **Emollient laxatives** e.g. liquid paraffin and dioctyl sodium sulfosuccinate.

ANTHRAQUINONE GROUP

The two most commonly used agents are *Cascara sagrada* and *Senna*. The active constituent anthraquinone is present as an inactive precursor glycoside in the leaves, pods and roots of these plants. Anthraquinone is present in a variety of other plants in the vegetable kingdom. On oral administration of extracts from these plants, the active anthraquinone derivatives mainly oxymethyl anthraquinones are liberated in the small intestine, where they are partly absorbed. These agents do not act on the small intestine, probably because the release of the active principle is too slow. However, sufficient quantity reaches the large intestine, via the blood as well as by intestinal propulsion of the unabsorbed portion from the small intestine. Anthraquinone acts by stimulation of the large bowel and also probably by inhibiting water absorption in the colon.

Pharmacological actions: As these drugs act mainly on the large bowel, evacuation occurs 6-8 hours after their ingestion. Stools are usually semisolid in consistency and the incidence of griping is low. There are no other important actions of absorbed anthraquinone derivatives. However, they are excreted in milk during lactation and this may produce diarrhoea in breast-fed infants. Some of the constituents are excreted in urine and colour the acid urine yellowish brown and alkaline urine reddish violet. The patient should be informed about this.

Between cascara sagrada and senna, the former is more bitter in taste while the latter produces more griping.

Aloe is the most irritant anthraquinone purgative and produces considerable griping and pelvic congestion. It is avoided during pregnancy. *Rhubarb*, in addition to anthraquinone, also contains tannin, which is responsible for producing after-constipation. Both aloe and rhubarb have no advantage over senna and cascara sagrada and are not recommended.

Adverse reactions: The only important toxicity of senna and cascara sagrada is excessive purgation and griping. Colic can be corrected by the administration of belladonna preparations. Rarely, chronic use of these compounds leads to benign melanotic pigmentation, of the colonic mucosa.

Preparations and dosage: Cascara sagrada I.P. is obtained from the bark of a tree *Rhamnus purshiana*. The available preparations are:

(i) Aromatic cascara sagrada fluid extract. Dose: 2-4 ml. at bed time.

(ii) Cascara sagrada liquid extract. Dose: 2-5 ml.

(iii) Cascara sagrada extract is a powdered preparation. Dose: 300 mg.

Both the dried Senna fruits I.P. (Senna pods) and dried Senna leaves I.P., obtained from the plants *Cassia acutifolia* and *Cassia angustifolia* respectively, are employed as laxatives. The dose in each case is 0.6 to 2 g. at bedtime. Other unofficial preparations are senna fluid extract, dose 2 ml. and senna syrup, dose 8 ml. Cathartic preparations containing purified Senna glycosides (Glaxenna), claimed to be more stable and reliable than the traditional preparations, are now available.

DANTHRON: This is a free anthroquinone with pharmacological properties and uses similar to those of natural anthraquinones.

IRRITANT OILS

CASTOR OIL: It is a fixed oil obtained by expression from the seeds of *Ricinus communis Linn.* Chemically, it is a triglyceride of ricinoleic acid, an unsaturated hydroxy-fatty acid. Castor oil itself is nonirritant and is many times used as hair oil or applied to skin as emollient. When ingested, it is hydrolysed in the intestine by pancreatic lipase to glycerol and ricinoleic acid. Ricinoleic acid acts as a mild irritant and produces purgation.

Pharmacological actions: As castor oil acts in the small intestine, it produces copious, liquid stools, with associated fluid loss. The action is quicker than that of anthraquinone and is evident within 2-3 hours. It causes griping. Ricinoleic acid that is absorbed is metabolized like any other fatty acid. The drug interferes with the absorption of various nutrients.

Castor oil I.P. is a pale yellowish or

almost colourless oil with peculiar odour and an initially bland but a nauseating after-taste. Dose 5 to 20 ml.

CROTON OIL: This is highly irritant and causes severe purgation and even death after as small a dose as 20 drops. It causes burning in the mouth, emesis and heamorrhagic gastroenteritis. The oil is only of toxicological interest.

RESINOUS CATHARTICS

This group includes agents like jalap, colocynth, podophyllum and elterin. The active ingredient is liberated in the small intestine where it causes severe irritation and produces copious watery stools, many times blood tinged, associated with severe griping. Overdosage leads to severe dehydration, prostration and collapse. These are no more used.

MISCELLANEOUS STIMULANT CATHARTICS

PHENOLPHTHALEIN: The discovery of phenolphthalein as a cathartic was purely accidental. In order to identify cheap wines, the Hungarian government ordered addition of this compound to such wines, since on the addition of alkali it turns brilliant red. The procedure was considered to be harmless. Those who took such sparkling drinks freely, obviously could not enjoy them as they suffered from diarrhoea.

Phenolphthalein, being an odourless and tasteless compound, forms the basic ingredient of many widely advertised preparations, dispensed in the form of chocolate or candy. Such preparations are very much in demand by the public.

Pharmacological actions: The mechanism of action is not known but the drug acts mainly on the large bowel after 6-8 hours and produces soft, semisolid stools, associated with a little griping.

The interesting aspect of phenolphthalein is that about 15 per cent of the dose is absorbed, some of which is re-excreted in the bile. This enterohepatic circulation of the drug causes prolongation of its cathartic effect.

The absorbed portion is excreted by the kidney mainly in the conjugated form. As the alkaline urine and faeces may get a reddish colour due to phenolphthalein, patients should be informed about this possibility.

Adverse reactions: Besides producing excessive purgation, phenolphthalein can sometimes cause marked colic, palpitation and even collapse. Deaths have been reported due to probable allergy to this drug. Allergic skin rash following this drug is not uncommon. It is characterised by pink to deep purple macular eruptions associated with itching and burning, rarely, even ulceration. The most undesirable aspect of this reaction is that the colourful lesions may persist for months or years and may even leave permanent residual pigmentation.

Since phenolphthalein has no distinct advantage over anthraquinone agents, except perhaps convenience of administration, it cannot be recommended as a drug of choice because of its possible toxicity.

Preparations and Dosage: Phenolphthalein is a white or a faintly yellow compound. Dose: 50 to 300 mg. at bed time.

BISACODYL (Dulcolax): This drug is structurally related to phenolphthalein and can be used orally and rectally in the form of suppository. It acts mainly on the large bowel. The mechanism of action is not known. The drug is not absorbed from the gastrointestinal tract and is claimed to be nontoxic. It is supplied as 5 mg. enteric coated tablets for oral administration and as 10 mg. rectal suppositories. The suppository is effective within 15 minutes to 1 hour after insertion.

CALOMEL (Mercurous chloride): This mercurial salt, once used extensively as a purgative, is now obsolete.

It is an unreliable purgative and if it fails to act, another cathartic is necessary to get rid of it. This is because appreciable amounts of mercury can get absorbed to produce systemic toxicity. Formerly, calomel formed an important ingredient of various 'teething powders' advertised for use in children. Chronic mercurial poisoning due to use of such powders was suspected as a major cause of Pink disease in children, with polyneuritis as a predominant feature.

OSMOTIC CATHARTICS

Certain salts, when given orally, are not much absorbed and are retained in the gastrointestinal tract. Such preparations exert an osmotic effect and, therefore, hold considerable amounts of water, thus increasing the intestinal bulk. This acts as a mechanical stimulus causing an increase in the intestinal motor activity and evacuation. The efficacy of the saline cathartic is, thus, related to the osmotic pressure exerted by the unabsorbed fraction within the intestinal lumen.

The commonly employed saline cathartics are magnesium, sodium and potassium salts.

Pharmacological actions: These compounds act in the small as well as the large intestines and, therefore, produce a watery evacuation within 3 to 6 hours. Because of their quick onset of action, they are given early in the morning before breakfast. They do not cause irritation and there is very little griping. Patients should be instructed to take plenty of water along with these drugs since administration of a hypertonic solution may produce dehydration due to water extraction from the circulation.

Small amounts of these drugs may get absorbed in the circulation and may cause occasional toxicity, particularly in the presence of kidney damage. Thus, the absorption of magnesium may cause marked central nervous system depression while that of sodium may worsen the existing congestive cardiac failure. In normal individuals, this is most unlikely as the small amount absorbed is rapidly excreted by the kidneys.

Preparations and Dosage:

(i) Magnesium sulfate, $7H_2O$. I.P. (Epsom salt)—crystalline, bitter salt, soluble in water. Dose: 2 to 16 g. Hypertonic solution is sometimes used rectally to reduce increased intracranial tension.

(ii) Dried magnesium sulfate is given in the dose of 2 to 12 g.

(iii) Milk of Magnesia is a 7.0 to 8.5 per cent acqueous suspension of magnesium hydroxide. Dose: 15 ml. It is less effective than magnesium sulfate.

(iv) Magnesium carbonate, heavy or light, I.P. is a hydrated basic magnesium carbonate. Dose: 2 to 4 g.

(v) Magnesium citrate is pleasant to take but is more expensive than magnesium sulfate. It is available as a flavoured solution. Dose: 200 ml.

(vi) Magnesium oxide heavy I.P. is a white powder. Dose: 2 to 4 g.

(vii) Sodium sulfate (Glauber's salt) occurs as colourless and odourless crystals with a bitter taste. It is less water soluble than magnesium sulfate. Dose: 2 to 16 g.

(viii) Sodium potassium tartrate (Rochelle salt) is administered in the dose of 8 to 16 g. Tartrate ion not being absorbed from the gastrointestinal tract, the compound does not produce systemic toxic manifestations.

(ix) Seidlitz powder is a mixture, in which 2.5 g. of sodium bicarbonate and 7.5 g. of Rochelle salt are dispensed together in a blue paper while 2.5 g. of tartaric acid is dispensed in a white paper. The user is asked to dissolve the contents of two papers separately in approximately 30 ml. of water and drink the mixture just after the effervescence begins to subside. The powders must not be taken separately. Carbon dioxide evolved by the reaction of sodium bicarbonate and tartaric acid is claimed to act as a carminative and to mask the unpleasant saline taste of Rochelle salt.

LACTULOSE: This is a synthetic nonabsorbable diasaccharide which acts by its osmotic effect. It is converted to lactic acid which can bind ammonia. Because of this ammonia binding property as well as its cathartic effect, lactulose is used in the treatment of hepatic coma. Lowering of colonic pH may be responsible for the laxative effect.

BULK LAXATIVES

These are various natural or semisynthetic polysaccharides and cellulose derivatives, which when given orally are not absorbed and increase the indigestible residue. These agents absorb water and swell up, thus providing the stimulus of mechanical distension for evacuation.

Pharmacological actions: These agents act purely because of their physical property. Their action is mild and is usually seen within 12-24 hours after ingestion. They produce evacuation of solid or semisolid stools without any irritation or griping. Some of these agents also have lubricating properties. Usually, these drugs are administered at bed time.

These drugs are not absorbed and do not have any systemic toxicity. Intestinal obstruction has been reported but is very rare.

Because these agents help to produce formed stools, they are also recommended in the treatment of diarrhoea. As many of these agents, when administered in a palatable form, can increase the bulk of undigestible material in the food, they have also been recommended in the treatment of obesity for satisfying appetite.

Preparations and Dosage:

AGAR: It is a mucilagenous substance extracted from marine algae. It contains indigestible hemicellulose. In contact with water, it forms a gel which has emollient or lubricating properties. The usual dose is 4 g.; occasionally, however, a dose as large as 40 g. may be required.

ISAPGOL I.P. consists of dried seeds of *Plantago ovata Forsk.* The seeds, which are hard and pinkish-grey to brown in colour, contain a large amount of natural mucilage. Dose: 5 to 15 g.

BRAN: It is the byproduct of the milling of wheat and contains almost 20 per cent of cellulose. Processed bran is palatable as such and it may be mixed with flour for preparing chapatis.

METHYL CELLULOSE, AND SODIUM CARBOXYMETHYL CELLULOSE are hydrophilic, semisynthetic derivatives of cellulose. The latter is insoluble in hydrochloric acid. Methylcellulose is administered in the dose of 1 g., 1 to 4 times daily, while sodium carboxymethyl cellulose is administered in the dose of 1.5 g., 1 to 4 times a day. The preparations should be taken with 30 to 40 ml. of water to minimize the risk of oesophageal obstruction. Generous amounts of water should be prescribed with all bulk purgatives.

Dietary fibre and bowel disorders: Unrefined plant products (fruits, vegetables, pulses, nuts and especially wholegrain products such as 100% whole-wheat flour and unpolished rice) are rich in indigestible cell wall materials. This material, known in the past as 'roughage' or 'residue' is now called 'fibre'. Chemically, this consists mainly of cellulose, hemicelluloses, pectins and lignin. Following ingestion, they hold water, form gels, exchange cations and bind bile acids. In the colon, they are mainly broken down to short-chain fatty acids, which may influence the colonic function favourably. Thus, the stool becomes heavier and softer so that the need to strain at stool is decreased. Occasionaly, frequency of defaecation may be increased. Increased intake of such fibre has been found useful not only in simple constipation but also in spastic colon, irritable bowel syndrome, colonic diverticular disease and anal fissures and piles. The best way of increasing the fibre-intake is to include fibre-rich foods in the diet. In persons who cannot or will not consume sufficient fibre rich food, wheat bran may be added to food or taken with water. Eating of raw fruits and certain raw vegetables may, however, often cause abdominal discomfort, bloating, griping and diarrhoea and should be avoided. Bran and other similar substances such as gum have been recently claimed to be useful in reducing hyperglycemia in diabetics, as well as plasma cholesterol. Their use for this purpose is under evaluation.

EMOLLIENT LAXATIVES

LIQUID PARAFFIN: It is the most widely used emollient laxative. It is a mineral oil consisting of a mixture of hydrocarbons obtained from petroleum. Given orally, it is not significantly absorbed and exerts a softening and lubricating effect on faeces.

Pharmacological actions: It is mild in action and in itself does not initiate peristalsis. Because of its lubricant action, the straining during defaecation can be avoided. It is usually given at bed time, but can be taken at any time of the day.

It is almost non-toxic but used repeatedly, it may interfere with the absorption of essential fat soluble substances and may cause a deficiency of vitamins A, D and K. The small amount which is absorbed from the intestinal tract may get deposited in the intestinal mucosa, liver and spleen and may, therefore, interfere with their functions. Rarely, it can cause lipoid pneumonia, if it gets into the lungs during its administration in bed-ridden patient and in old people.

Preparation and dosage: Liquid paraffin I.P. is a colourless, transparent, oily liquid. Dose: 8 to 30 ml.

Edible oils like coconut oil, ground nut oil, cotton seed oil and corn oil can also be employed as lubricant purgatives. The usual dose is 30 ml. or more. These oils, however, are digested and hence, fairly large doses are needed for lubricant effect.

SURFACE ACTIVE LAXATIVES

DIOCTYL SODIUM SULFOSUCCINATE: This drug, which is used in pharmaceutical industry as a dispersing agent, acts by its physical property of lowering surface tension. It does not stimulate peristalsis but is claimed to promote softening of faeces. The evidence for therapeutic superiority of this drug over other well established preparations is lacking. In animals, the drug is known to interfere with wound healing.

Dose: 50 to 300 mg. It should not be combined with liquid paraffin as it may enhance the absorption of the latter.

Uses of cathartics:

(1) In the treatment of constipation. They are often misused for this purpose. See below.

(2) In food or drug poisoning, to flush the intestinal tract. Saline cathartics are generally preferred.

(3) Following anthelmintic therapy, to eliminate the parasites; saline cathartics are preferred.

(4) Pre-operatively in abdominal surgery or prior to radiological examination of the abdomen. Routinely, castor oil is used but other mild stimulant cathartics may also be employed.

(5) In patients with anal fissure, piles, typhoid, cardiac disease and in pregnant women, in order to avoid excessive straining during defaecation. In these conditions lubricant laxatives like liquid paraffin and vegetable oils are recommended.

Irritant cathartics should be avoided during pregnancy as these may cause pelvic congestion although abortion following therapeutic doses of cathartics is most unlikely. Similarly, these drugs should also be avoided in case of typhoid fever and in very ill cardiac patients; in such patients, if satisfactory evacuation fails to occur following lubricant laxatives simple enema may be employed. Cathartics are absolutely contraindicated in patients with undiagnosed acute abdomen and in cases with intestinal obstruction as violent contractions may lead to intestinal rupture and subsequent peritonitis.

CONSTIPITION AND CATHARTICS

Constipation may be defined as "functional impairment in the inherent capacity of the colon to produce normally formed stools at regular intervals." Individuals are known to differ widely in the 'normal' habits concerning the frequency, quantity and consistency of stools and missing a bowel movement does not necessarily affect the health. Failure to realise this many times leads to self medication and to cathartic habit. In most cases, 'constipation' is functional and can be corrected by simple measures such as increasing the roughage in the diet and water intake, exercise and treatment of emotional factors, if any. The proper 'habit time' should be developed and the natural reflex, when it occurs, must not be ignored routinely. The bulk residue can be increased and stools can be softened by simple measures such as increasing bran or leafy vegetables in the diet or by using bulk purgatives like isapgol, methyl cellulose or agar agar. Such measures are particularly useful in patients with irritable bowel syndrome, who may complain of constant or intermittent symptoms with the passage of small, round 'rabbit' or 'sheep' stools and abdominal pain aggravated by fatigue, smoking and mental tension. The pain could be related to the ingestion of certain foods such as coffee, spices, fried foods, certain vegetables and fruits and even milk. Only in a few cases of chronic constipation, mild stimulant purgatives from the vegetable group may be necessary in initial stages. In old or obese individuals and in convalescing patients who find it difficult to strain, lubricant drugs or suppositories are useful while in those in whom spastic colon is suspected, use of belladonna preparations may be beneficial. Constipation associated with diseases like vitamin B_1 deficiency or hypothyroidism will be corrected following vitamin B_1 or thyroxine therapy.

Constipation in infants and children sometimes poses a problem. In many cases, however, it is exaggerated by the anxious parents who believe that a daily good evacuation is necessary for good health. It is essential, therefore, that parents, particularly mothers, should know that the dire consequences of constipation are mostly imaginary. It is known that breast fed babies may sometimes have infrequent stools, once every four days, without any abnormal symptoms. This obviously needs no treatment. In artificially fed babies, hard stools are often produced because of under-feeding or deficient intake of water and sugar in the feeds; the water requirement in warm countries like India is usually more than that in the temperate zones. In such cases, increasing the water intake and adding more sugar to feeds corrects the constipation. Occasionally, however, one has to prescribe a laxative particularly in those children in whom passing of hard stools is associated with considerable discomfort. The drugs usually advocated are magnesium hydroxide mixture (Milk of magnesia) or mild vegetable cathartics like senna or cascara in a syrupy base. Suppositories containing glycerine may be prescribed when other methods are not helpful. It acts by its hygroscopic action within 10-20 minutes. It is reliable, safe and cheap. In some cases with really formidable constipation, enemas are necessary to clear the bowel.

Cathartics used occasionally are not harmful but their repeated administration may produce:

(1) Gastrointestinal disturbances like spastic colitis, dyspepsia, anorexia and nausea.

(2) Nutritional deficiency of calories, vitamins, and minerals due to interference with their absorption.

(3) Loss of fluid and electrolytes, particularly potassium and calcium, giving rise to hypokalemia and osteomalacia.

(4) Complete dependence on drugs and later even resistance to all the mild purgatives, due to the development of spastic colon.

(5) Selective toxicity due to certain drugs used.

It should be remembered that after a thorough evacuation following a purgative, it may take some days to normalise the bowel movement and individuals should be told about this. Otherwise, they may feel that the constipation is continuing and would repeat the purgative, which may lead to the development of 'habit'.

It is important that family physicians should counter the false notions created in the minds of lay people, many times by commercial advertisements, and must emphasize the limitations of purgatives rather than prescribe them loosely, whenever the patient complains of 'constipation'. Further, it is advisable to carry out an abdominal and rectal examination to exclude any local rectal or anal lesion.

In the clinical management of persistent constipation, it is very essential to exclude possible local organic disease. In patients with primary intestinal pathology and secondary constipation, the treatment does not consist of giving purgatives but the attention to primary disease is of utmost importance.

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Pharmacotherapy of Peptic Ulcer

Peptic ulcer, one of the common gastrointestinal diseases, is largely a disease of adult males. Women seem to be peculiarly immune to peptic ulceration during the child-bearing age.

Gastric ulcers occur most frequently in the older age group and in the lower socio-economic class of individuals. Duodenal ulcers, on the other hand, commonly occur in younger individuals and are evenly distributed among various socio-economic groups.

The exact cause of ulceration is not known. The gastric acid and pepsin, however, are definitely known to be responsible for maintaining the lesion, once it is produced. Peptic ulceration occurs only in areas which are bathed by an acid juice and it is true to say, "No acid, no ulcer". In certain individuals, there is a constitutional tendency to produce hyper-secretion of gastric juice and acid. As this tendency persists even after the healing of an ulcer there is always a chance of recurrence and hence the uncertainty about its ever being permanently cured.

Factors modifying gastric acid secretion: The gastric juice, as collected by a tube, is a mixture containing hydrochloric acid, pepsin, rennin (in children), neutral chlorides, mucus, intrinsic factor and traces of potassium, ammonium and calcium.

The gastric acid and pepsin are secreted by the main gastric glands, present all over the body and fundus of the stomach. The rate and the composition of secretion from main gastric glands vary considerably, depending upon such factors as the number of acid secreting cells (the parietal cell mass), emotional factors, digestive state at a given time, the hormonal status and the presence of extrinsic chemical stimuli such as caffeine and histamine.

Hydrochloric acid is secreted by the 'oxyntic' cells lining the main gastric glands. The precise mechanism of hydrochloric acid formation is not clear. The pure secretion of the oxyntic cells consists of 0.5 normal hydrochloric acid. The gastric juice, however, is much less acid than this as a result of several factors such as rate of gastric emptying, dilution by the food, and neutralization by the mucus, food and the alkaline contents regurgitated from the duodenum.

Columnar cells lining the entire gastric mucosa secrete an alkaline mucus gel which exerts a protective action against the acid and pepsin. The secretion of columnar cells increases in response to mechanical stimuli, while vagal stimulation and histamine have no effect.

The pyloric glands, present in pyloric antrum, secrete (a) gastrin, directly into the blood, and (b) an alkaline, viscid mucus-rich juice, into the stomach. Gastrin stimulates the production of acid gastric secretion.

The 'chief' cells of the gastric glands secrete pepsinogen, which is activated at acidic pH below 6 to the enzyme pepsin. Optimal activation occurs at pH 2. Enzyme and acid secretion in the stomach generally varies in parallel manner.

Normal gastric acid secretion is essential as it acts as a chemical barrier to bacterial invasion and is important for the maintenance of optimum pH at 1.5 to 4 necessary for the action of pepsin. Activity of pepsin is markedly reduced at pH above 4 and almost ceases at pH 5.

Phases of gastric secretion: It is now customary to express the gastric acid secretion in m. equiv./hour.

(a) *Basal secretion*; During the inter-digestive period, acid is secreted at the rate of 2-4 m. equiv/hour in normal individuals. This, measured as nocturnal acid secretion, is high in most patients with duodenal ulcer but may be normal or even low in patients with gastric ulcer. It can be completely blocked by anticholinergic drugs and H_2 receptor antagonist.

(b) *Secretion in response to food*: Gastric secretion in response to food may be divided into two phases, neurogenic and hormonal.

In *neurogenic* or *cephalic phase*, the secretion occurs as a result of sight, smell, taste or even simple thought of food. The juice secreted is highly acidic and rich in pepsin. This secretion is mediated by the vagus and abolished by vagotomy and is only partially blocked by anticholinergic drugs. Alterations in the gastric secretion induced by emotions are also mediated neurogenically. In man, depression and fear result in a suppression of gastric secretion, whereas anger and resentment result in increased production. Violent emotions cause congestion and hyperemia of the gastric mucosa, rendering it more susceptible to traumatic ulceration.

In *hormonal phase*, the gastric secretion is increased due to stimulation of the oxyntic cells by *gastrin*. The major chemical stimulus for the release of gastrin is the presence of protein in the food entering the stomach. In addition, alcohol, caffeine (present in coffee, cola drinks, etc.). vagal stimulation and mechanical stimulation of the stomach cause gastrin release. A cocktail before dinner or a protein broth soup before a meal stimulates acid secretion and prepares the stomach for the main dish! On the other hand, a high concentration of acid (very low pH) in the antral region directly inhibits gastrin release. In addition, like gastric motility, gastric secretion is inhibited by reflexes initiated in the duodenum by distension, hypertonic solution, fatty acids, amino acids and acid in the duodenum. Thus, high fat content of a meal may inhibit gastric emptying to 4-6 hours whereas a meal containing carbohydrate and proteins may leave the stomach in 2-3 hours. Fat in the duodenum acts as a stimulus for the release of gut hormone *cholecystokinin* (CCK) whereas acid in the duodenal chyme is an effective chemical stimulus for the release of another gut hormone *secretin*. Both secretin and CCK via circulation inhibit the stomach motility and glandular secretion. The hormonal phase is inhibited only partially by anticholinergic drugs but substantially by H_2 receptor antagonist.

Natural gastrin is a polypeptide believed to contain 17 amino acids. A synthetic pentapeptide **Pentagastrin,** containing mainly four amino acids (tryptophan, methionine, phenylalanine and aspartic acid) produces secretory and other biological actions similar to those of the natural gastrin. Thus, pentagastrin stimulates the secretion of acid, pepsin, intrinsic factor and pancreatic enzymes. It also stimulates the intestinal smooth muscle and increases intestinal motility. Pentagastrin is used clinically as a diagnostic agent to study the gastric secretory response in the diagnosis of conditions like pernicious anemia, duodenal ulcer, and to study the gastric response following vagotomy for duodenal ulcer. It is preferred to histamine.

Pentagastrin is given subcutaneously, intramuscularly or intravenously. It is ineffective orally. Occasionally, it causes nausea, retching, fainting and hypotension.

Chemical stimulation of gastric secretion: Histamine stimulates the secretion of gastric juice which is highly acidic but poor in pepsin content. As this is similar to gastrin-induced secretion, gastrin is suspected to act on oxyntic cells through the liberation of histamine locally. Histamine is used to test the maximum ability of the stomach to secrete acid (Kay's augmented histamine stimulation test).

Adrenal glucocorticoids probably play a permissive role in the gastric acid secretion.

Patients with duodenal ulcer as a group have (1) higher capacity to secrete acid and pepsin probably due to larger parietal cell mass, (2) higher sensitivity to gastrin so that they respond with hypersecretion to submaximal stimulus by pentagastrin, (3) incomplete inhibition of gastrin release at low pH in the antrum, (4) rapid gastric emptying and (5) larger acid load to the duodenum. Why this is so is not known.

Principles of peptic ulcer therapy: As the precise cause of peptic ulcer is not known, therapy is still empirical. It consists of:

(1) Controlling gastric acidity, hypermotility and spasm and thus relieving the associated pain.

(2) Promoting ulcer healing and

(3) Prevention of complications and recurrence.

Control of gastric acidity may be achieved by one or more of the following methods:

(a) Use of antacids, milk or ion exchange resins.

(b) Stimulating the release of CCK by means of a fatty meal or a vegetable oil. The latter, given at bed time, is fairly effective in controlling the nocturnal pain.

(c) Inhibiting gastric acid secretion by drugs.

(d) Withdrawal of stimulants of gastric acid secretion such as alcohol, caffein, tobacco and soft cola drinks. Cessation of smoking has been demonstrated to promote ulcer healing.

(e) Surgical removal of the acid producing gastric mucosa by gastrectomy or abolition of the vagal effects on acid secretion by vagotomy.

GASTRIC ANTACIDS

Gastric antacids are chemical substances which, on ingestion, react with gastric acid and lower the acidity of gastric content. They produce a symptomatic relief of pain, partly by reducing the acidity and partly by the consequent relief of muscle spasm. Reduction in acidity inhibits the action of pepsin. Antacids are thus expected to promote healing.

If adequate relief of symptoms in duodenal ulcer is to be brought about without seriously interfering with peptic digestion of food, the gastric pH must be raised from the usual level of 1-2 to between 3.5 and 4.5. Although this is possible with antacids, it is difficult to maintain it continuously at that level. Hence, to achieve even a reasonable control of gastric acidity, regular and frequent administration of an antacid round the clock would be necessary, which is inconvenient for obvious reasons.

In spite of these limitations, antacids are valuable, for they produce considerable symptomatic relief in patients with duodenal ulcer and in cases with gastritis.

Mechanism of action: These drugs act as weak bases. They raise the gastric pH to above 4. Certain antacids like sodium bicarbonate can theoretically raise the gastric pH above 7.

There is no good evidence that any of the antacids 'physically adsorb' H^+ ions over and above the acid they can neutralize chemically.

Classification: Antacids are commonly divided into:

(1) **Non-systemic antacids:** such as aluminium hydroxide gel, magnesium trisilicate, magnesium hydroxide, magnesium oxide, calcium carbonate, bismuth carbonate and calcium phosphate. Of these, drugs like magnesium trisilicate, aluminium hydroxide and aluminium phosphate gel are sometimes called as 'Buffer antacids' as they do not raise the gastric pH above 4.5 while drugs like magnesium oxide, hydroxide and calcium carbonate are sometimes designated as 'Non buffers' as they are believed to raise the pH even above neutrality. This, however, is not true in practice as none of these drugs raises the pH above 5 and in this respect, therapeutically they are indistinguishable. These drugs are water insoluble, generally unabsorbable and are called non-systemic because they do not produce systemic alkalosis.

(2) **Systemic antacids:** Compounds like sodium bicarbonate and sodium citrate are absorbed into the systemic circulation and may cause alkalosis. Hence, they are called 'systemic antacids'.

(3) **Miscellaneous:** gastric mucin and protein hydrolysates.

Because of the varying rates of acid neutralization by various antacids, comparison of the amount of acid neutralized per gramme of the antacid does not give valid information about its relative clinical efficacy. The figures of 'm. equiv. of acid neutralized per gramme or per ml. of the antacid' represent the acid neutralized when the reaction is completed. In certain instances, the antacid may leave the stomach before the reaction is complete.

NON-SYSTEMIC ANTACIDS

These are water insoluble and generally unabsorbable preparations. In the stomach, the cation of the antacid forms a chloride during neutralization of the acid. In the alkaline pH of the small intestines, the chloride salt reacts with the bicarbonate from the intestinal juices to regenerate the original salt (hydroxide or carbonate). There is, thus, no net gain or loss of H^+ or HCO_3^- ions to the body. Hence, systemic alkalosis is avoided. In the case of calcium and magnesium salts, formation of soaps also helps to prevent alkalosis by binding these salts with organic acids in the intestinal lumen.

Non-systemic antacids are insoluble till they come into contact with the acid. Some of the antacid which escapes the reaction with the acid remains in the stomach and reacts with the acid subsequently secreted. The duration of action of such insoluble antacid is, therefore, generally longer than that of soluble antacids.

ALUMINIUM HYDROXIDE GEL: This is available either as a white, colloidal, viscous suspension or as dried gel in the form of powder or tablets. It reacts with gastric acid to form aluminium chloride. Thus,

$$Al(OH)_3 + 3HCl \rightarrow AlCl_3 + 3H_2O$$

Each ml. of 4 per cent gel suspension neutralizes 1.2 to 2.5 m. equiv. of acid. The neutralizing action, however, is slow, more so in the case of dried gel. Moreover, the acid neutralizing capacity has been found to differ according to the process of manufacture and age of the product and to vary from batch to batch in the case of a given product. The gastric pH is raised to 4. Pepsin activity is not significantly inhibited.

In the intestines, $Al(OH)_3$, is regenerated from $AlCl_3$, and chloride liberated is reabsorbed.

In man, aluminium hydroxide has no effect on the volume of gastric juice nor on the total output of hydrogen ion. The nocturnal secretion is also not affected. It has, however, astringent and demulcent properties by which it forms a protective coating over the ulcer crater. It may also adsorb toxins, gases and bacteria.

Adverse reactions: Constipation is the only major side effect. This is easily countered by combining aluminium hydroxide with magnesium trisilicate or by giving liquid paraffin. Aluminium hydroxide may prevent the absorption of phosphate from the intestines. This may rarely lead to osteomalacia. The drug may interfere with the absorption of certain agents like tetracyclines, iron salts, anticholinergic drugs, corticosteroids and P.A.S.

Other uses: It can also be used to reduce intestinal absorption of phosphate in cases with phosphatic renal calculi and in chronic renal failure with rickets.

Preparations and dosage: Aluminium hydroxide gel 4-8 ml. every 2-4 nours. In nephrolithiasis and in chronic renal failure 40 ml. four times a day.

ALUMINIUM PHOSPHATE GEL: It is sometimes preferred to aluminium hydoxide gel, as it does not interfere with phosphate absorption. It has, however, no special advantage. It is available as an aqueous suspension containing 3.8-4.5 per cent of the drug.

DIHYDROXYALUMINIUM AMINOACETATE: It has been claimed to be a faster acting drug. It is available as suspension containing 100 mg./ml. or 0.5 g. tablets.

MAGNESIUM TRISILICATE: It is available as a fine, white, colourless, tasteless powder, insoluble in water. In the stomach, it reacts with acid to form hydrated silicon dioxide.

$$Mg_2Si_3O_8 . nH_2O + 4HCl \rightarrow$$
$$2MgCl_2 + 3\ SiO_2 + (n + 2)\ H_2O$$

As it becomes gelatinous in consistency, it provides a protective coating to the ulcer crater.

The neutralizing action of magnesium trisilicate is slow in onset but prolonged. It has no effect on the amount of acid secreted. In the intestines, magnesium chloride reacts with the bicarbonate to form magnesium carbonate, which is excreted in feces; about 7 per cent is absorbed and excreted in the urine.

Hydrated silica gel has adsorbent properties similar to those of aluminium hydroxide gel.

One gramme of magnesium trisilicate neutralizes about 9-11 m. equiv. of gastric acid.

Adverse reactions: It may cause mild diarrhoea.

Dose: 2-4 g. every 1-4 hours. The tablet should be chewed before it is swallowed because it does not distintegrate rapidly in the stomach.

CALCIUM CARBONATE: It occurs as a white, tasteless, odourless powder with a chalky taste. In the stomach, it reacts with gastric acid to form calcium chloride. Thus,

$$CaCO_3 + 2HCl \rightarrow CaCl_2 + H_2O + CO_2$$

In the intestines, $CaCl_2$ reacts with bicarbonate to regenerate $CaCO_3$, which is excreted in feces.

$$CaCl_2 + 2NaHCO_3 \rightarrow$$
$$CaCO_3 + 2NaCl + H_2O + CO_2$$

Calcium carbonate acts quickly. It has a high neutralizing capacity and the action is prolonged. It is inexpensive. Some authorities believe it to be the most effective antacid. One gramme of the drug neutralizes 13 m. equiv. of acid.

Adverse reactions: It has a tendency to produce constipation and fecal concretions. Hence, it is sometimes used in combination with light magnesium carbonate and bismuth carbonate (Pulv. tricarb). Magnesium salt is expected to counteract the constipating effect. Calcium carbonate increases serum gastrin level and gastric acid secretion above the basal level. During prolonged therapy, it has been reported to cause hypercalcemia with associated systemic complications.

Dose: It is given as powdered precipitated chalk or tablets containing 1 g. of calcium carbonate.

MAGNESIUM OXIDE AND HYDROXIDE: Magnesium oxide, on contact with water, is converted to magnesium hydroxide and then acts. Magnesium hydroxide combines with the gastric acid:

$$Mg(OH)_2 + 2HCl \rightarrow MgCl_2 + 2H_2O$$

In small intestine, $Mg(OH)_2$ is regenerated and excreted in feces.

It is a quick acting antacid and the action is prolonged.

Magnesium oxide is available as a light, colourless water insoluble powder. One gramme neutralizes 50 m. equiv. of the acid. The dose is rather bulky.

Magnesium hydroxide is available as 'Milk of magnesia' containing 7 to 8.5 per cent of magnesium hydroxide. One ml. of milk of magnesia neutralizes 2.7 m. equiv. of acid.

Adverse reactions: Magnesium hydroxide has a mild cathartic action which can be countered by combining it with a calcium salt.

Although a small amount of magnesium is absorbed into the blood, it produces toxicity only in the presence of impaired renal function. The toxicity is characterised by central nervous system depression.

Dose: As an antacid: 4 ml. of milk of magnesia. As a laxative: 15 ml. of milk of magnesia.

MAGNESIUM CARBONATE: This antacid has properties similar to those of magnesium hydroxide except that carbon dioxide is liberated during neutralization of the acid. One gramme neutralizes 20 m. equiv. of acid. It has been shown to be an excellent antacid in clinical practice, perhaps even superior to calcium carbonate.

It forms a constituent of the commonly used 'Pulv. tricarb'.

SYSTEMIC ANTACIDS

SODIUM BICARBONATE: Sodium bicarbonate is a white, water soluble and completely absorbable antacid.

It reacts with the gastric acid according to the reaction,

$$NaHCO_3 + HCl \rightarrow NaCl + H_2O + CO_2$$

One gramme of the drug neutralizes 12 m. equiv. of acid.

In the intestines, sodium chloride remains unchanged and is unable to neutralize the bicarbonate of the intestinal contents. The latter is, therefore, absorbed causing systemic alkalosis.

It is an effective and rapidly acting antacid. Its duration of action, however, is short. Eructation of the carbon dioxide liberated during the process of acid neutralization often gives the patient a sense of relief from abdominal discomfort. This is the basis of its reputed carminative action. In the presence of a gastric ulcer, excessive carbon dioxide liberation may rarely lead to perforation. Contrary to past belief, carbon dioxide does not stimulate further acid secretion and there is no sound basis for the so-called 'acid rebound' phenomenon.

During continuous, frequent administration of sodium bicarbonate in sufficient quantities, the output of the gastric juice and acid far exceeds the basal secretion. This is probably because the continuous maintenance of raised pH in pyloric antrum stimulates gastrin liberation.

Adverse reactions: Short duration of action and the occasional risk of gastric perforation make sodium bicarbonate a much less useful drug than what it would otherwise be. Systemic alkalosis and possibility of edema due to sodium retention are its other disadvantages.

Uses: (1) Peptic ulcer: Dose 2 g. every hour for continuous action.

(2) To combat metabolic acidosis.

(3) To render urine alkaline in the treatment of certain urinary tract infections and to prevent precipitation of substances such as sulfonamide and uric acid.

(4) For topical use: Solution of sodium bicarbonate is used as an antipruritic lotion, as an eye wash, mouth wash, douche, to loosen wax in the ear and in enemata.

SODIUM CITRATE: Sodium citrate has properties similar to those of sodium bicarbonate except that there is no liberation of carbon dioxide. It is a common constituent of many commercial preparations advertised for gastrointestinal distress. Dose 1-4 g.

Effervescent preparations that 'fizz' consist of sodium bicarbonate and citric acid which react in solution, producing carbon dioxide and sodium citrate.

MISCELLANEOUS DRUGS

BISMUTH SALTS: The preparation presently advocated is colloidal tripotassium dicitrate bismuthate. It is claimed to be useful in reducing acidity in gastric and duodenal ulcers.

PROTEIN HYDROLYSATES: These are used in the hope that the amino acids would act as antacids. In the form in which they are present in such mixtures, they are only moderately effective as antacids. After an initial buffering action, they stimulate gastric acid secretion. Hence, when used, they should be given along with other antacids.

Protein hydrolysates, when given in

adequate doses (upto 250 g/day), definitely improve the nutritional status of a peptic ulcer patient; this can contribute to healing of the ulcer.

POLYAMINE METHYLENE RESIN: It is a cation exchange amine resin containing secondary and tertiary amine groups in the lattice of a large, insoluble, resin molecule. In the stomach, the amino groups combine with hydrogen ions to form ammonium groups. In the small intestines, the hydrogen ion is given up and amino groups are reformed.

The resin has a low acid neutralizing capacity, is bulky and unpalatable. It may cause nausea, vomiting and diarrhoea. It is also expensive. It is not commonly employed in practice.

ANTACID THERAPY

Being advertised to the laity and sold over the counter without doctor's prescription, gastric antacids are among the most abused drugs. Their indiscriminate use without an attempt to establish the cause of 'dyspepsia' can sometimes lead to masking of the warning symptoms of a serious condition like cancer of the stomach. However, when used properly and in adequate doses, they help to relieve the pain of peptic ulcer. When used under strict hospital conditions, where repeated measurements of gastric acidity are carried out to monitor antacid therapy, they also probably contribute to ulcer healing.

While using antacids it is necessary to remember certain important aspects of their pharmacology. Thus, (1) In the fasting state antacids have only a transient intragastric buffering effect, about 15-30 minutes. When ingested 1 hour after meal, however, they have a much more prolonged effect of about 3-4 hours. Therefore, they should be prescribed in optimal dose at 1 and at 3 hours after meal for continuous effect.

(2) The *in vivo* buffering effect of an antacid does not necessarily correlate with its *in vitro* effect. Some antacids are potent *in vivo* buffers while others are not. The physician, therefore, should be thoroughly familiar with the properties of a few selected antacids.

(3) The quantity of an antacid required to produce optimal buffering varies from one patient to another. As a general rule, patients with hyper-acid-secretion as in DU require larger quantities than the hyposecretors such as those with gastric ulcer, and

(4) Antacid tablets, though more convenient than liquids, are less effective buffers and must be thoroughly chewed for maximal efficacy. Liquids are to be preferred for the management of patients with active ulcer disease.

Choice of the antacid: Systemic antacids should be avoided. Aqueous suspensions of non-systemic antacids are more effective than dried preparations of the same substances. Among the commonly used antacids, calcium carbonate, magnesium carbonate, magnesium oxide and magnesium hydroxide are considerably more effective than magnesium trisilicate, which, in turn, is more effective than aluminium hydroxide. Antacid mixtures do not produce better results than antacids used individually. Side effects of drugs such as constipation should be treated with an appropriate drug in each individual patient. Alleged demulcent, astringent, pepsin inhibiting or other non-antacid properties of the drug do not contribute significantly to their therapeutic effectiveness in peptic ulcer. Hence, only the antacid property of the various drugs should be considered while choosing an antacid.

An ideal antacid:

(1) should act quickly and should have a prolonged action.

(2) should not liberate carbon dioxide or cause rebound secretion.

(3) should not interfere with the digestion of food.

(4) should not cause alkalosis,

(5) should be nontoxic, palatable, cheap and easily available.

GASTRIC ACID SECRETION INHIBITORS IN PEPTIC ULCER

ANTICHOLINERGIC DRUGS: These drugs are used mainly for their antimuscarinic effects on

(1) the gastric acid secretion and

(2) the gastric motility, in the hope of relieving pain and promoting ulcer healing. Belladonna and its alkaloid atropine have been used for this purpose for many years and the newer compounds claimed to be superior must be compared with this established drug. In case of quaternary ammonium compounds like propantheline, additional ganglionic blocking action may contribute to the therapeutic benefit obtained.

These drugs are discussed in detail in Chapter 16. Only their actions which are pertinent to peptic ulcer therapy are discussed here.

Experimentally when adequate doses are used parenterally, anticholinergic drugs effectively inhibit the basal gastric acid secretion; insulin hypoglycemia and histamine induced acid secretion are relatively resistant. However, adequate drug concentration is difficult to achieve with the generally used oral therapeutic doses. Clinical evidence indicates that tension type of ulcer pain which is relatively uncommon may be relieved but the commoner pain related to the food ingestion, which is effectively relieved by antacids, is little affected. This later type of pain is probably related to acid secretion.

Anticholinergic drugs certainly inhibit gastric motility and prolong the gastric emptying time. This increases the stay of an antacid in the stomach and increases its effectiveness; in the absence of effective antacid therapy, it would prolong the contact of the acid secretion with the ulcer. This would lead to aggravation of the symptoms. They are more useful in duodenal ulcers than in gastric ulcers. In the presence of pyloric stenosis, however, these drugs may cause gastric retention.

Therapeutic benefit from anticholinergic drugs occurs only in doses which produce at least some systemic side effects. In fact, the degree of dryness of mouth is a useful indication of the efficacy of a given dose. These drugs have to be administered frequently to get a continuous effect.

Peptic ulcer is a capricious disease with a natural tendency for spontaneous remissions and exacerbations. Even close clinical supervision and treatment with a placebo often promote improvement without the addition of special medication. Pain, a purely subjective symptom, is the most important clinical feature of peptic ulcer. Objective evidence of ulceration in the form of radiological demonstration of the ulcer crater is often difficult to obtain. Its absence does not necessarily indicate complete healing. These factors make the clinical evaluation of an anticholinergic drug very difficult. Available evidence indicates that anticholinergic drugs are more useful in relieving nocturnal pain which is difficult to control with antacids. There is no evidence that their continued use prevents a recurrence of the ulcer, which is the most decisive index of therapeutic efficacy of such drugs. The beneficial effects obtained with these agents do not seem to be sustained and complications are not always prevented. In general, despite the physiological rationale, clinically these drugs offer only a marginal benefit in the treatment of duodenal ulcer.

Choice of an anticholinergic drug: From the published evidence, it is difficult to choose the best drug. The absence of CNS toxicity with quaternary ammonium compounds (see Chapter 16) gives them some advantage, their gastrointestinal absorption, however, is irregular and their renal excretion is rapid, resulting in a short duration of action.

Anticholinergic drugs are not a substitute for the established therapy of peptic ulcer but only adjuvants to measures like bed rest, diet and antacid therapy. They have to be used with caution in the presence of suspected pyloric obstruction, glaucoma, prostatic hypertrophy and anginal heart disease. In future, these drugs are likely to be replaced by H_2-receptor antagonists.

CIMETIDINE (Tagamet): This H_2-receptor antagonist is chemically closely related to its earlier predecessor metiamide except that it has a cyanoguanidine group instead of the thiourea group (See Chapt. 20). Like metiamide it markedly inhibits the basal and meal stimulated gastric secretion, but has a longer duration of action than metiamide. Atropine, though an inhibitor of gastric acid secretion, decreases meal-stimulated acid secretion by approximately 30-50 per cent only, even when prescribed in optimally effective doses. Cimetidine has, however, a wider spectrum of inhibition in that it inhibits markedly (80-90%) histamine, pentagastrin and insulin stimulated gastric acid secretion in man. Present evidence indicates that the drug promotes ulcer healing in man. On oral administration, cimetidine reduces the gastric secretion of acid to about 20 per cent within an hour and food does not seem to interfere with its action. The effect is mainly on the volume of secretion; in the patient eating normally and taking four doses daily, gastric pH nevertheless remains below 2 for much of the time. Addition of anticholinergic drugs does not augment the effects of cimetidine. It has a minimal action on intrinsic factor secretion.

Given orally, it is well absorbed and the therapeutic effect of a single dose lasts for 5-8 hours. It is substantially excreted in the urine within 24 hours, mostly as unchanged drug. It can cross the placenta and is excreted in milk.

Adverse reactions: These appear to be mild and include rashes, diarrhoea, and muscle pain. Hepatotoxicity, gynecomastia and agranulocytosis have been reported though rare. It must be noted, however, that histamine and H-receptors are widely distributed in various areas such as heart, blood vessels, bone marrow, pituitary gland, hypothalamus and other areas in brain and in certain subgroups of T-cell lymphocytes. Hence, further data is needed to define its long term safety, and also effectiveness in preventing the relapse of peptic ulcer.

Preparations and dosage: The drug is available as 200 mg tablet and as injection. In cases with duodenal ulcer it is usually given in the dose of 200-300 mg twice or thrice daily, immediately after meals plus 400 mg at bed-time, for a period of 4-8 weeks. Second course may be repeated if relapse occurs. During therapy it is advisable to check the serum creatinine concentration.

Therapeutic uses: It is used in the treatment of duodenal ulcer. It appears to be less effective in promoting the healing of gastric ulcer. Cimetidine has also been used successfully to treat multiple peptic ulcers due to gastric hypersecretion from excessive circulating gastrin (Zollinger-Ellison syndrome) and stress induced ulcers. It may also be useful in peptic oesophagitis.

PROSTAGLANDIN E_2: Human gastric mucosa contains prostaglandin E_2 (PGE_2). Given intravenously, PGE_2 inhibits gastric acid secretion in man but its exact physiological role is uncertain. It is not effective orally. One of the synthetic analogues of 15 methyl prostaglandin E_2, however, when given orally inhibits basal and pentagastrin stimulated gastric acid and pepsin secretion. Further, it has been shown to stimulate the mucus secreting cells of the gastric mucosa. In rats, the drug could prevent gastric and oesophageal ulcers. Recently, 15 methyl PGE_2 has been administered orally in the dosage of 150 μg. 6 hourly in Chinese subjects suffering from gastric ulcers with beneficial results. The therapeutic usefulness of various PGE_2 analogues in the management of gastric ulcers need further evaluation.

MANAGEMENT OF PEPTIC ULCER

The management of peptic ulcer is essentially medical. Surgery is indicated when

(a) malignancy is suspected in a gastric ulcer,

(b) a duodenal ulcer becomes chronic and produces intractable symptoms refractory to prolonged and efficient medical management,

(c) a complication such as organic obstruction or perforation is present, and

(d) the patient suffers from repeated attacks of gastrointestinal haemorrhage.

The medical treatment consists of rest, dietary restriction, antacids, anticholinergic drugs, sedatives and withdrawal of such agents as tobacco (smoking) and caffeine (in beverages). In recent clinical studies simple measures like the bed rest and stoppage of smoking have clearly shown to promote ulcer healing. Use of the drug carbenoxolone also accelerates the gastric ulcer healing while allowing the person to continue his normal daily activities. Use of H_2-receptor antagonist cimetidine appears to be beneficial in duodenal ulcer but therapeutic benefits of carbenoxolone are uncertain. An initial period of bed rest is, therefore, advisable in patients with recent ulcers and in those with severe symptoms.

(a) **Diet:** During the active stage, diet should consist of small, frequent, bland meals taken every 2-3 hours. Spices, chillies and fried foods should be avoided. Edible vegetable oils, ghee and butter taken as such are helpful, as these have an inhibitory effect on gastric acid secretion. Milk drip has often been found to help in relieving symptoms when other methods have failed.

(b) **Antacids and antisecretory drugs:** These are administered as discussed previously.

(c) CARBENOXOLONE SODIUM (Biogastrone): Carbenoxolone sodium is a pentacyclic triterpene prepared from the liquorice glucoside glycyrrhizic acid. The drug possesses a special anti-inflammatory action similar to that of corticosteroids, without any antianabolic effect. It does not affect the carbohydrate metabolism but like mineralocorticoids, it may cause retention of sodium and water with increased excretion of potassium.

Oral administration of carbenoxolone has been shown to be beneficial in promoting healing of gastric ulcers in patients eating a normal diet and continuing at work. Its exact mode of action is not known, but it probably acts by stimulating mucus secretion and thus providing protection to the base of the ulcer against gastric acid and pepsin. Mucus is known to adsorb pepsin and combine with acid. However, the possibility that carbenoxolone also stimulates the collagen activity in the base of an ulcer and/or stimulates epithelization cannot be ruled out. It is also claimed to inhibit the activation of pepsinogen to pepsin. It has little effect on gastric acid production or motility of the stomach. Recent work with this drug administered in capsules which disintegrate only in pylorus, thus discharging the contents into duodenum, has suggested that it may also promote healing of duodenal ulcer. Further experience, however, is necessary before its definite place in the therapy of duodenal ulcer is established.

Absorption, fate and excretion: Carbenoxolone is rapidly absorbed from the stomach and is largely excreted in the bile. The biliary metabolites, consisting of glucuronide and sulphate conjugates of carbenoxolone, are reabsorbed in the intestines.

Adverse reactions: It causes water and sodium retention and potassium depletion. These are generally not marked but may occasionally cause congestive cardiac failure in elderly subjects with heart disease. Hence, it should be avoided in elderly patients. It is unwise to try to counter the adverse effects by using diuretics because aldosterone inhibitors inhibit its effect on the gastric mucosa and thiazides may aggravate the hypokalemia. Sometimes, it causes headache, heartburn and hypertension. Some of the toxic effects of carbenoxolone sodium could be due to its high protein binding property which displaces the mineralo-corticoids from non-receptor proteins. It is possible that other steroids have their effects potentiated by a similar mechanism.

Preparations and dosage: It is a white, hygroscopic powder soluble in water. The drug is usually given in a dose of 50-100 mg. three times a day, after meals, for 4-8 weeks. If healing does not occur surgery should be considered as there is a distinct possibility of the gastric ulcer being malignant. Administration of milk may reduce heartburn.

Crude liquorice which contains this ulcer-healing factor has also been used successfully in the treatment of gastric ulcer.

Other uses: The drug, in the form of lozenges containing 5 mg., has been found to be useful in intractable aphthous ulcers in the mouth.

(d) **Sedatives and tranquilizers:** Drugs like phenobarbitone are routinely used in the treatment of peptic ulcer. These, along with a sympathetic discussion of the patient's problems, may be useful in relieving the anxiety and tension. Formal psychotherapy, however, has not been shown to produce any dramatic effects.

(e) AMYLOPECTIN SULFATE (Depepsen): This synthetic sulfated polysaccharide reduces the peptic activity and there is some evidence that its use may promote healing of gastric ulcers. Its use is experimental at present.

(f) GAFARNATE: This is an interesting drug derived from the juice of white-head cabbage. It is a lipid soluble substance related to vitamin A. It has been claimed to promote the healing of primary gastric ulcer. Its mode of action is unknown. The drug needs further evaluation.

Therapeutic benefits of gefarnate and amylopectin in the treatment of duodenal ulcer are uncertain.

When treated adequately, relief of symptoms in recent ulcers occurs within 7-10 days. This does not, however, necessarily mean that ulcer has healed and treatment has to be continued for some weeks after relief of symptoms. Failure to respond to medical treatment indicates chronicity or the presence of complications such as stenosis or perforation into neighbouring viscera such as pancreas. A gastric ulcer may undergo malignant change.

No treatment available at present, however meticulously carried out, can guarantee against a recurrence of the peptic ulcer. Hence, patients should be advised moderation in living and eating, and to avoid smoking, drinking and taking certain drugs in the hope of preventing a recurrence. The drugs to be avoided are salicylates, butazones, reserpine, aminophylline, caffeine, para-amino salicylic acid and other gastric irritants. Increased gastric acidity and increased incidence of duodenal ulceration, bleeding and perforation are noted during pharmacological (as opposed to replacement) therapy with glucucorticoids; hence, these drugs should be administered cautiously in patients with suspected peptic ulcer.

Section XI: Oxytocics and Uterine Relaxants

39 Pharmacology of Ergot Alkaloids, Oxytocin, other Oxytocics and Uterine Relaxants

Ergot or *Claviceps purpurea* is a fungus which grows mainly on rye and occasionally on other grains. Ergot spores, carried by insects or wind, are deposited on the ovaries of young rye where they germinate and their hyphal filaments penetrate deep into the ovary of the rye. This results ultimately in destruction of the entire grain substance and formation of a hardened, black purple body termed the sclerotium, which serves as the commercial source of ergot. Consumption of ergot-infected rye was the cause of the disease termed *St. Anthony's fire*, observed in middle ages and characterised by dry gangrene of extremities and a high incidence of abortions and stillbirths in pregnant women; a visit to St. Anthony's shrine was thought to be curative and hence the name. An outbreak of ergot poisoning was recorded as recently as in 1953 in France.

ERGOT ALKALOIDS

Chemistry of ergot alkaloids: Ergot has been termed a treasure house of pharmacological constituents. The most important of these are the alkaloids. In addition, active components like histamine, tyramine and acetylcholine are also present in ergot. Other constituents include steroids, acids, quaternary ammonium bases and inorganic compounds.

Only the levorotatory forms of the ergot alkaloids are pharmacologically active. These can be divided into:

I. **The amino acid alkaloids:** These are ergotamine, ergosine and ergotoxin. The last, formerly thought to be a single alkaloid, has been found to be a mixture of three alkaloids, ergocornine, ergocristine and ergokryptine.

II. **The dihydrogenated amino acid alkaloids:** These are dihydroergotamine (DHE) and hydergine, the latter being a mixture of dihydroergocornine, dihydroergocristine and dihydroergokryptine.

III. **The amine alkaloid:** Ergometrine (ergonovine).

Pharmacological actions:

(a) **Uterus:** All the natural ergot alkaloids have the ability to cause contraction of the uterine smooth muscle. The response depends upon the alkaloid employed, the dose used and the degree of uterine maturity and stage of gestation. Thus, the amino acid alkaloids elicit a delayed but powerful response; their dihydrogenated derivatives, however, are active only on pregnant uterus at term. Ergometrine and its derivative methylergometrine elicit an immediate and powerful response. Small doses produce an increase in the force of contraction, with normal relaxation in between consecutive contractions. With larger doses, the resting muscle tone increases, the contractions become more powerful, tetanic, and frequent. Still higher doses cause a sustained contracture. The amino acid and the amine alkaloids are capable of stimulating the uterus during any phase of estrous cycle or gestation, and even an immature uterus is stimulated, but in general the uterus at full term and immediately after delivery is highly sensitive. A small dose of the amine alkaloids in any of these cases produces a marked contraction of the uterus with minimum side effects.

The amine alkaloid ergometrine has several advantages over the amino acid alkaloids such as ergotamine. Thus, it is devoid of significant adrenergic blocking, vasoconstrictor and emetic activity. Further, it is effective orally and elicits a prompt contractile response. Also, it is less toxic.

Ergot alkaloids increase the tone of the cervix in contrast to oxytocin which decreases it. Further, the frequency of contractions is increased more with ergot alkaloids than with oxytocin.

(b) **Vascular actions:** The adrenergic blocking action of the amino acid alkaloids has been discussed in Chapter 14.

In addition to their adrenergic blocking activity, they possess direct vasoconstrictor effect. Peripheral vasoconstriction is accompanied by damage to the capillary endothelium, particularly with large doses. Ergotamine is the most potent vasoconstrictor. The dihydrogenated amino acid alkaloids are powerful alpha adrenergic blocking agents and their direct vasoconstrictor effect is minimal, except in the case of DHE, which, in addition to alpha adrenergic blockade, also produces significant vasoconstriction. In contrast to the amino acid alkaloids, the amine alkaloid ergometrine has no adrenergic blocking activity and causes minimal vasoconstriction.

(c) **Gastrointestinal tract:** Ergotamine increases peristaltic activity and can potentiate the action of neostigmine on the gut.

(d) **Miscellaneous:** The amino acid as well as the amine ergot alkaloids are potent 5-HT antagonists. Methysergide, a clinically useful 5-HT antagonist is a derivative of ergometrine.

Absorption, fate and excretion: The amino acid alkaloids like ergotamine and the dihydrogenated derivatives are erratically absorbed from the gastrointestinal tract. Ergometrine and methylergometrine, on the other hand, are rapidly and completely absorbed; their oxytocic effect is seen within 10 to 15 minutes of oral, 3 to 5 minutes of subcutaneous and 1 to 2 minutes of intravenous administration.

The fate of the ergot alkaloids is not definitely known. They are probably metabolised in the liver and the degradation products eliminated in urine. Liver damage enhances the toxicity of ergot compounds.

Adverse reactions: Toxicity of amino acid alkaloids and their dihydrogenated derivatives has been discussed in Chapter 14.

Ergotamine and ergotoxin are more toxic than the dihydro derivatives. Toxicity may develop during prolonged therapy and is mainly due to direct vascular actions leading to thrombosis and gangrene. Treatment consists of immediate withdrawal of the drug, use of antiemetic drugs and belladonna alkaloids for the treatment of emesis and administration of anticoagulants like heparin and vasodilator agents like tolazoline and sodium nitroprusside, for the treatment of peripheral vascular insufficiency. Good nursing care is imperative if gangrene of an extremity develops. Ergometrine and methyl-ergometrine may produce nausea and vomiting but serious toxic effects are rare. Their injudicious use during the 1st and 2nd stage of labour may, however, result in death of foetus in utero or rupture of the uterus.

Preparations and dosage:

(i) Preparations of ergotamine and dihydroergotamine (See Chapter 14).

(ii) Ergometrine tablet I.P. contains 0.5 mg. of ergometrine maleate. Dose: 0.5 to 1 mg.

(iii) Ergometrine injection I.P. contains 0.5 mg. of the drug per ml. Dose: 0.2 to 1 mg. intramuscularly and 0.1 to 0.5 mg. intravenously.

(iv) Ergotamine tartrate 0.25 mg. with ergometrine maleate 1.25 mg. injection (Neogynergen) though not official, is also available. Dose: 1 ml. I.M.

(v) Methylergometrine tablet N.F. (Methergine) contains 0.125 mg. of methylergometrine maleate. Dose: 0.25 to 0.5 mg.

(vi) Methylergometrine injection N.F. contains 0.2 mg. of the drug per ml. Dose: 0.2 mg. by subcutaneous, intramuscular or intravenous route.

Therapeutic uses:

(i) **Postpartum hemorrhage:** Ergometrine and methyl-ergometrine are extremely useful in both prophylaxis and treatment of postpartum hemorrhage. For prophylaxis, they may be administered at the end of the second stage following crowning of the head or appearance of the anterior shoulder at the vulva, or at the beginning of the 3rd stage after the delivery of foetus, when they hasten the expulsion of the placenta, or after the completion of labour. An intramuscular dose of 0.2 to 0.3 mg. is usually employed. If immediate action is desired an intravenous dose of 0.2 mg. is given. However, intravenous administration may result in dangerous hypertension, particularly when vasopressor drugs or spinal anaesthesia are being employed concomitantly or if the patient is pre-eclamptic. In abortion, where the loss of foetus is inevitable, ergometrine may be employed to control bleeding.

(ii) **Uterine involution:** Ergometrine, in the dose of 0.2 mg. orally thrice daily, is employed for 7 days after childbirth to hasten the process of uterine involution, although the beneficial effect of this agent on the normal process of involution is not yet established. It is, however, useful in the same dose in cases of delayed involution where it hastens involution, prevents bleeding and checks the spread of infection.

(iii) **Hypertension:** Only the dihydrogenated derivatives are used. The use of hydergine in the treatment of hypertension is discussed in Chapter 26.

(iv) **Migraine:** Migraine is a syndrome characterised by paroxysmal headache secondary to local spasm and painful overdistension of the cranial and extracranial arteries. It shows a strong hereditary tendency. Attacks of headache may be triggered off by a variety of exogenous factors like impending menstruation and relaxation after emotional tension. The headache is classically unilateral, may vary in duration from a few minutes to many days and in 10 to 15 per cent of cases, it is preceded by a variety of visual and neurologic abnormalities such as scintillating scotomata and visual field defects. These are often accompanied by nausea, vomiting, diarrhoea and prostration. Very rarely, migrainous headaches are due to structural lesions in the CNS like an aneurysm or an angioma.

The multiplicity of treatments available and the large number of drugs used in treating this condition indicate the non-availability of a single effective drug in its treatment. Further, because of the periodic nature of this disorder, it is difficult to assess the efficacy of drugs claimed to be effective.

In all cases of migraine, aspirin should be given a trial and many patients may not need any other therapy. Ergotamine tartrate, administered during the attack, is effective in abolishing the headache due to migraine in approximately 90 per cent of cases. DHE may be used for this purpose but postural hypotension is a troublesome side-effect. It must be emphasised that other adrenergic blocking agents are not useful in migraine. These drugs do not prevent the attack of migraine and, on the contrary, may precipitate such an attack if administered during the prodromal period. They are of little value in non-migrainous headaches. Given subcutaneously in the dose of 0.5 mg., ergotamine tartrate usually produces relief within 15 minutes; occasionally a period of 1 to 2 hours is required. In less acute cases, oral or sublingual route may be employed. The oral dose is 4 to 5 mg. initially and 2 mg. every hourly thereafter; if relief is not obtained even with 8 mg., 0.5 mg. of the drug may be administered subcutaneously. The total combined dose, however, should not exceed 10 mg. If such full dose is given within a 24 hour period, the drug should not be repeated for a week, as it may cause toxicity. The sublingual dose is 3 to 4 mg. initially followed by 2 mg. hourly till a quantity of 10 mg. is administered. Oral medication produces relief within 4 to 5 hours and may not be effective in a severe attack. The intravenous route is dangerous and is used rarely; the initial dose by this route is 0.35 mg. and not more than 0.5 mg. should be administered within 24 hours. DHE is administered by subcutaneous or intramuscular route in the dose of 1 mg.

Caffeine is claimed to enhance the action of ergotamine and various proprietary preparations containing ergotamine and caffeine are available. Xanthines (caffeine) also constrict cerebral blood vessels and reduce the cerebral blood flow.

Oral diuretics may prevent attacks secondary to fluid retention in the premenstrual period.

Ergotamine and DHE, because of their vasospastic and oxytocic activities, are contraindicated in the presence of gangrene, peripheral vascular diseases, coronary artery disease and advanced atherosclerosis. Ergotamine should be avoided in the presence of pregnancy, hypertension and hepatic and renal disease.

Other drugs, *methysergide* and *clonidine* used in therapy of migraine, are discussed in Chapter 21 and 26 respectively.

BROMERGOCRYPTINE: See Chapter 61.

Other Oxytocics

The posterior pituitary extract shows two distinct pharmacologically active principles, namely vasopressin which acts on the kidney and the blood vessels and oxytocin, which has a dominant action on the uterus and the myoepithelium of the mammary gland. The pharmacology of vasopressin is discussed in Chapter 34.

OXYTOCIN: This is an octapeptide usually represented in the following simplified form:

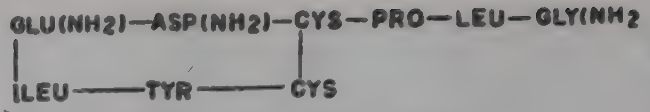

Fig. 39.1: Oxytocin.

The polypeptide is freely soluble and acid stable. A synthetic preparation with identical structure and pharmacological actions is also available.

Formation and release of oxytocin: Oxytocin and vasopressin are synthesized in hypothalamic nuclei. They travel along hypothalamus-hypophyseal tract to the posterior lobe of the pituitary where they are stored and from where they are released under a variety of stimuli. These include dehydration, hemorrhage, dilatation of the cervix and uterus and emotional stimuli. As both oxytocin and vasopressin are bound to a common protein, all these stimuli cause a simultaneous release of both the hormones.

Pharmacological actions:

I. **Uterus:** The oxytocic activity of the posterior pituitary hormones varies according to the dose, the species, the stage of estrous cycle and in a pregnant animal, according to the stage of gestation. Thus, the uterus of a virgin guinea pig or that of a virgin rat in diestrus is much more sensitive to oxytocin than the non-pregnant human uterus. These effects are highly dependent on the presence of estrogen. In the early period of pregnancy in humans only very high doses are effective. However, as the pregnancy advances, from 5th to 6th months onwards, the sensitivity of pregnant uterus to oxytocin increases rapidly.

Oxytocin, in small doses, exerts a physiological action on the pregnant uterus. The effect is the result of a direct stimulation of the uterine smooth muscle. The upper uterine segment, consisting of the fundus and body, is contracted while the lower uterine segment, consisting of the cervical portion is dilated and this results in an expulsion of the fetus from the uterine cavity. The contractions also squeeze the maternal blood out of the placenta into the maternal inferior vena cava. The periods of relaxation which intervene between the two successive contractions allow refilling of the placental blood vessels by the maternal arterial blood and thus prevent asphyxial injury to the foetus. Oxytocin, therefore, can be used by slow intravenous infusion for inducing labour at term in contrast to ergot preparations which are contra-indicated.

With high doses of oxytocin, the uterine tone increases, the contractions become more powerful and frequent and asphyxial injury to the child may develop as a result of direct compression and ischemia caused by inadequate filling of the placental blood vessels.

II. **Mammary gland:** The myoepithelium, a modified smooth muscle, which surrounds the alveolar ramifications of the mammary gland is stimulated by oxytocin resulting in an expulsion of milk from the alveolar lumen and ducts into large cisterns and sinuses This is termed milk ejection or milk 'letdown'. The milk ejection reflex is initiated by the stimulus of suckling, which results in the release of oxytocin.

III. **Cardiovascular system:** The cardiovascular actions of vasopressin are discussed elsewhere. Oxytocin, in small doses, produces a vasodilator effect in man by direct relaxation of the vascular smooth muscle. A transient hypotension, particularly diastolic, and flushing accompanied by tachycardia are usually observed in man. The usual infusion rates employed in obstetrics do not modify the blood pressure. The vasodilator effect of oxytocin can be readily blocked by small amounts of vasopressin. The hypotensive phase is followed by a rise in blood pressure which is probably due to an increase in the cardiac output. Oxytocin given intravenously in large doses abolishes leptazol induced arrhythmias in dogs and arrhythmias induced by general anaesthetics in man.

IV. **Kidney:** Synthetic oxytocin has been demonstrated to possess antidiuretic activity in man and a dose of 100 milliunits causes a definite antidiuresis in postpartum women; this is associated with a diminution in the renal plasma flow and the GFR. The renal effects of oxytocin may be due to constriction of renal cortical vessels in the presence of oestrogens.

Absorption, fate and excretion: Oxytocin given orally is inactivated by trypsin.

The aqueous solution, on intramuscular administration, is absorbed rapidly. The half life of the hormone in normal humans is about 10 to 15 minutes. The removal from the circulation is due mainly to the kidneys and the liver. Plasma from men and nonpregnant women does not inactivate oxytocin but the plasma, the uterine tissue and the placenta in pregnant women contain an enzyme termed 'oxytocinase' which probably inactivates oxytocin. The plasma oxytocinase levels are elevated early in pregnancy and then decline slowly from 4th month onwards. The functional significance of oxytocinase is not clear. The half-life of oxytocin in pregnant women is approximately 3 minutes.

Besides the parenteral route, oxytocin is absorbed from the nasal and buccal mucous membranes. Absorption from these routes, however, is erratic.

Adverse reactions: Deaths due to 'pituitary shock', observed following the use of posterior pituitary extracts during labour, are now attributed to vasopressin. Oxytocin given intravenously may occasionally cause water retention leading to water intoxication. It is characterised by nausea, vomiting, anorexia, weight gain and lethargy. Injudicious use of oxytocin during labour may result in premature birth, foetal death, too rapid a delivery or uterine rupture.

Preparations and dosage:

(i) Posterior pituitary injection I.P. is a sterile aqueous extract of the posterior lobe of mammalian pituitary bodies. It contains 10 oxytocic units per ml. Dose. 0.2 to 0.5 ml. (2 to 5 units) by subcutaneous or intramuscular injection.

(ii) Oxytocin injection IP. is a sterile, aqueous solution containing the oxytocic principle of the posterior lobe of the mammalian pituitary body. It is standardized to contain oxytocic activity equivalent to 10 units per ml. The pressor activity in the solution must not exceed 0.5 pressor unit per ml.

(iii) Synthetic Oxytocin injection (Syntocinon) contains 10 oxytocic units per ml. It is as active as the natural compound and does not contain vasopressin.

(iv) Oxytocin citrate buccal tablets (200 U.S.P. units each) for sublingual administration.

Bioassay of oxytocin: The oxytocic activity of the posterior pituitary extract is bioassayed *in vitro* by its ability to produce contraction of one horn of the uterus of a virgin guinea pig. Alternatively, it can also be assayed by its ability to produce a fall of blood pressure in a chick.

Therapeutic uses: Oxytocin is usually preferred to the crude posterior pituitary extract as the latter may produce anaphylactic shock on intravenous administration. Further, a dangerous aggravation of hypertension may result when the crude extract is administered to hypertensive, pre-eclamptic or eclamptic women and the presence of ADH activity may cause oliguria.

(i) **Induction of labour:** For the induction of labour, oxytocin is usually administered intravenously as an infusion, 2 to 5 units in 500 to 600 ml. of 5 per cent dextrose solution. To start with, approximately 0.5 ml. of the solution should be given per minute; the rate is then gradually increased to a maximum of 2 ml. per minute. During the whole procedure, the uterine response should be closely observed and a vigilant watch should be maintained on the foetal heart rate.

(ii) **Uterine inertia:** Oxytocin is occasionally employed to initiate uterine contractions in cases of prolonged, stubborn and hypotonic uterine inertia. Before using oxytocin, cephalopelvic disproportion must be ruled out. Multiparous patients (para 4 and over) and those with uterine scars should not receive oxytocin for induction, for the fear of uterine rupture. In all cases, the dose should be carefully regulated and a close watch on foetal heart rate be maintained.

(iii) **Postpartum hemorrhage:** Oxytocin is routinely administered either subcutaneously or intramuscularly in the dose of 2 to 5 units after the delivery of placenta to produce a firm contraction of the uterus and thus prevent postpartum hemorrhage. The drug may also be administered in the same dose after delivery of the anterior shoulder of the foetus to produce a prompt expulsion of the placenta and to prevent postpartum hemorrhage. The same amount may also be injected directly into the uterus, after delivering the foetus by caesarean section.

(iv) **Abortion:** Oxytocin is employed in the dose of 20 to 30 units by intravenous infusion to induce therapeutic abortion during the 2nd or the 3rd trimester of pregnancy. The drug may be used subcutaneously, intramuscularly or intravenously to complete an incomplete abortion.

(v) **Miscellaneous:** Oxytocin may be given intranasally in the dose of 40 units 2-3 minutes before breast feeding to promote milk ejection when this component of lactation appears to be deficient in nursing mothers.

SPARTEIN SULFATE: Spartein is an alkaloid obtained from the flowering broom. The alkaloid was originally employed in the treatment of cardiac arrhythmias but the dosage required was high and approached the dose which depressed both the rate and the contractility of cardiac muscle. In addition, when used in high doses, it has nicotine-like actions on the autonomic ganglia and the skeletal muscles.

Spartein has an oxytocic activity on both pregnant and non-pregnant human uterus. However, there is a marked variability in the uterine response to this drug from one woman to another and even in the same woman. In large doses, the drug causes tetanic contractions of the uterus.

Spartein sulfate (Unitocin) is usually

administered intramuscularly in the dose of 100 to 600 mg. It is quickly inactivated in the body, though less rapidly than oxytocin. Uterine contractions produced do not simulate the normal labour. Foetal injury, cervical lacerations and uterine rupture can occur following its use. Its superiority over oxytocin has not been established.

PROSTAGLANDINS: Prostaglandins are C_{20} fatty acids containing a cyclopentane ring.

Actions of prostaglandins are described in Chapter 21; only the effects on uterus are discussed here.

Apart from human seminal fluid PGs are found in the ovary, myometrium and menstrual fluid. Their physiological significance, however, is not well understood. Majority of prostaglandins in varying doses, inhibit the spontaneous activity of isolated non-pregnant human myometrium. However, PGF and PGF$_2$, and PGE in low doses, stimulate both the tone and amplitude of the uterine contraction. Recently, four prostaglandins have been isolated from human amniotic fluid, obtained during normal labour and during spontaneous abortion. Furthermore, prostaglandin F$_2$ was also found in samples of blood obtained during normal spontaneous labour but not during other stages of gestation. Since prostaglandin F$_2$ has smooth muscle stimulating action it is possible that it participates in the process of labour. Experimentally they are shown to sensitize the uterus to oxytocin as well as causing oxytocin release.

These drugs can stimulate uterine contractions at any stage of pregnancy. Prostaglandins, PGF$_2$ and PGF, E$_2$ and E$_1$ have been used to induce labour and to terminate the pregnancy.

Adverse reactions: These are not troublesome with smaller doses but could be severe with larger doses. They include nausea, vomiting, headache, diarrhoea and fever. Vasodilatation may occur.

Preparations: (1) Prostin F$_2$ α is available as a solution in 4 and 8 ml ampoules containing the equivalent of 5 mg. of PGF$_{2\alpha}$ per ml for use by intra-amniotic route to induce abortion. (2) Dinoprostone (Prostin E$_2$) is supplied as 0.75 ml ampoules containing 1 mg per ml solution in ethanol. The contents of the ampoule can be added to normal saline for dilution.

Therapeutic uses:

(1) *Induction of labour*: Dinoprostone may be preferred for this purpose to oxytocin in the presence of chronic renal failure or pre-eclampsia, because of its diuretic action. Apart from this, it offers no significant advantage over oxytocin; it is more expensive and less well tried than the latter. It is administered as an intravenous drip with normal saline at the rate of 0.25 μg. per minute, increasing gradually to a maximum of 1.0 μg. per minute if satisfactory uterine contractions do not occur with smaller doses. Signs of uterine hypertonus and foetal distress should be watched for. The adverse effects of dinoprostone with this dosage are usually mild.

(2) *Therapeutic abortion*: Dinoprostone can be used to terminate the pregnancy in the second trimester and for evacuating uterus in the presence of missed abortion or hydatidiform mole. However, much larger doses are needed for this purpose. Hence, adverse effects could be severe and the evacuation may not be complete in all the cases. It is usually given by intra-amniotic route by means of a Foley catheter. The dose of PGF$_{2\alpha}$ used is 25 mg. repeated, if necessary, in 6 hours. This route should not be used in the presence of cervical or vaginal infection. Dinoprostone can also be given by intravenous route, in a drip with normal saline; the dose needed varies between 2.5 and 10 micrograms per minute.

Intravaginal administration of prostaglandin, though effective, causes marked systemic adverse effects and the therapeutic results are unpredictable.

HYPERTONIC SALINE: There is really no absolutely safe method for terminating pregnancy in the second trimester. Introduction of various irritants into the uterine cavity for this purpose, as done by the quacks, is usually associated with serious complications and even death.

Intra-amniotic injection of hypertonic 20% saline appears to be quite effective and reasonably a safe procedure for terminating the pregnancy. Usually 100-250 ml. of amniotic fluid is withdrawn through a transabdominal approach and equal amount of hypertonic saline is injected. This causes severe damage to the placenta and foetal death. Labour usually starts within 24-36 hours after the injection resulting into complete abortion in 70% of cases. The systemic absorption of sodium may sometimes cause headache, thirst, increased B.P. and congestive cardiac failure.

Recent comparison between hypertonic saline and $PGF_{2\alpha}$ (intra-amniotic) for induction of second trimester abortion revealed equal effectiveness with similar frequency of incomplete abortion or excessive bleeding.

UTERINE RELAXANTS

In contrast to oxytocics, uterine relaxants are of limited value in therapeutics. Numerous agents including atropine, ephedrine and adrenaline are capable of inducing uterine relaxation. Their effect, however, is transient and varies widely according to the species, stage of the estrous cycle and presence or absence of gestation.

Drugs capable of inducing relaxation of human uterus include isoxsuprine, orciprenaline and anaesthetics like ether and halothane. Salbutamol, a selective $beta_2$ receptor stimulant has been used by continuous intravenous infusion to delay delivery in premature labour with some success. The other drugs tried are orciprenaline, ritodrine and fenoterol. These drugs are discussed elsewhere. The uterine relaxant effect of magnesium sulfate, given in therapeutic doses in humans, is equivocal.

Recent evidence indicates that progesterone. even on intra-amniotic administration in pregnant women, fails to achieve significant uterine relaxation. Relaxin, a water soluble protein or polypeptide extracted from the corpus luteum of pregnant sows, and claimed to cause relaxation of pubic symphysis and softening of the uterine cervix has been used in the treatment of premature labour, uterine inertia and cervical dystocia but appears to be of doubtful value.

Section XII: Chemotherapy

40

Sulfonamides, Nitrofuran Compounds, Nalidixic Acid and Trimethoprim

The word 'Chemotherapy' can be defined as the use of chemical compounds in the treatment of infectious diseases, so as to destroy infective parasites or organisms without damaging the host tissues. The evolution of chemotherapy can be traced through 3 distinct periods, a pre-Ehrlich era before 1891, the period of Paul Ehrlich, and the period after 1935 highlighted by the discovery of sulfonamides and antibiotics.

In the long pre-Ehrlich era, many compounds were employed in therapeutics purely empirically, occasionally with beneficial and often with hazardous consequences. Thus, usefulness of Cinchona bark in the treatment of malaria and mercury in syphilis was known for many years. With the advances in chemistry and microbiology in the renaissance period, a great variety of infective organisms were identified and isolated.

Paul Ehrlich (1854-1915), an organic chemist, was struck by the fact that certain vital dyes like methylene blue specifically killed and stained certain bacterial cells and he reasoned that chemical substances might be produced that could unite with and destroy the parasitic agents of disease without in any way injuring the host cells. He aptly called them as "magic bullets". In 1891, he demonstrated the efficacy of methylene blue in the treatment of human malaria. He also synthesized a series of arsenical compounds effective against syphilis and other spirochaetal infections. To express the therapeutic utility of these compounds he introduced the term '*chemotherapeutic index*', a ratio of the maximum tolerated dose of a drug to its minimum curative dose. This index has now been replaced by the *therapeutic index* expressed as LD_{50}/ED_{50}.

Ehrlich postulated that the cell membrane contained specific chemical groups or 'receptors' which combined with essential materials like oxygen and caused their uptake by cells. He visualised a drug as containing a chemical grouping or '*heptaphore*' that enabled the drug to get attached to the cell receptor and another grouping termed '*toxophore*' which enabled the drug to produce its specific pharmacological effect. A drug could exert either a curative or a toxic effect depending upon its affinity for the parasite or the host. Thus, a compound with a high affinity for the host tissue, an *orgánotropic* compound, could be toxic while one with high affinity for parasites, a *parasitotropic* compound, might be curative. Based on this hypothesis, Ehrlich introduced arsephenamine, the first really effective chemotherapeutic agent in man, in the treatment of syphilis.

The pioneer work of Ehrlich established the importance of cellular chemistry in drug action and inspired many workers to synthesize newer and more powerful antibacterial substances. Ehrlich is aptly called 'the Father of Modern Chemotherapy'. He was awarded a Nobel prize in 1909.

The next major contribution to chemotherapy came from Domagk, Mietsch and their colleagues (1938), who, while working on azo dyes, demonstrated the efficacy of 'Prontosil', a dye with a sulfonamide side-chain, in inhibiting the growth of Streptococci both *in vitro* and *in vivo*. Nitti, Bovet and Fuller proved that Prontosil owed its therapeutic efficacy to its conversion into sulfanilamide in the body. Since then a variety of sulfonamides have been synthesized. It is interesting to note that sulfanilamide was prepared by Gelmo as early as 1908 but 30 years elapsed before its therapeutic value was discovered.

The idea of using one micro-organism to cure the infection caused by another was repeatedly suggested during the last century. Thus, Pasteur and Joubret in 1877 demonstrated that 'common bacteria' prevented the growth of anthrax bacilli in urine, and Babes in 1885, using solid culture media, established that one bacterium could elaborate a substance that would stop the growth of another. Emmerich and Low in 1899, while working on the organism *Pseudomonas aeruginosa,* discovered that extracts of this organism in high dilutions could destroy a variety of pathogenic cocci, as well as diphtheria, cholera, typhoid and plague organisms.

In 1928, Sir Alexander Fleming, while studying staphylococcal variants, found one of his culture plates contaminated by a fungus (eventually identified as *Penicillium notatum*) which prevented the growth of surrounding bacterial colonies. He cultivated the fungus in a broth and showed that the filtrate, which he named penicillin, inhibited the growth of a number of Gram positive organisms. This compound was not toxic to animals and was devoid of local irritant properties. The discovery of penicillin, however, remained for a long time more or less a scientific curiosity. The work of Chain, Falk and Florey in 1941 during the 2nd World War established penicillin as the most potent anti-infective agent. In 1945, Fleming, Chain and Florey were awarded the Nobel Prize for this revolutionary contribution. The 6-aminopenicillenic acid nucleus of penicillin was isolated in 1959 and this has led to the development of a variety of semisynthetic penicillins.

In 1944, after more than ten thousands micro-organisms had been screened, Schatz, Bugie and Waksman reported the isolation of streptomycin from *streptomyces griseus,* found in a diagnostic culture from a chicken's throat. Waksman also defined the term 'antibiotic' as *"a chemical substance produced by micro-organisms having the property of inhibiting the growth of or destroying other micro-organisms in high dilution."* This last clause is necessary to exclude such metabolic products as organic acids, alcohol and hydrogen peroxide. This was a major advance, as Streptomycin, unlike penicillin, was found to be effective against Gram negative organisms, and also against *Mycobacterium tuberculosis.* Since then, a large number of antibiotics have been developed and tested for their efficacy against various organisms.

The vital factors in determining the efficacy of chemotherapeutic agents are the presence of natural body defence mechanisms and the development of resistance by the micro-organisms to the particular agent. Host plays an important part in the curative action of most of the specific remedies.

A chemotherapeutic agent may act by destroying the organism (bactericidal) or by inhibiting its growth (bacteriostatic). The selective toxic action on the infecting organism is the key to beneficial actions of antibiotics. These drugs can hit at least four targets in bacteria namely, the cell wall, the cytoplasmic membrane, the ribosomes and the molecules involved in transcription of genetic information.

The cell wall of bacteria is a thick rigid envelope, mainly composed of sugar and peptides called mucopeptide or murein. The mucopeptide is much thicker in gram-positive cells than in gram-negative cells. Underneath the rigid cell wall is a cytoplasmic membrane which encloses the cytoplasm. This membrane has lipo-protein structural elements, which account for selective permeability to water, ions and nutrients. Antimicrobials attacking this membrane may alter the permeability of the cell or may disorganize the lipoproteins leading to cell death.

Inside the cytoplasm are ribosomes, spherical particles, which are concerned with protein synthesis. Ribosomes act as an assembly line where aminoacids are joined together into peptide chains and proteins. The process is directed by messenger RNA (mRNA), which carries the code for such synthesis from the nuclear DNA. Messenger RNA becomes attached to ribosomes where the transcribed code is translated into appropriate protein synthesis. Antimicrobials can bind to ribosomes and may interfere with peptide chain formation in bacteria or with the transcription mechanisms.

Mechanisms of action of various antibiotics are summerized in table 40.1.

Table 40.1: **Mechanisms of Action of Antimicrobial Agents**

Interference with cell wall synthesis

Penicillins, Cephalosporins, Bacitracin and Cycloserine.

Damage to the cytoplasmic membrane

Polymyxins, Colistin and Polyene antibiotics.

Inhibition of protein synthesis and impairment of the function of ribosomes

Aminoglycosides, Tetracyclines, Chloramphenicol, Macrolide antibiotics and Lincomycin.

Interfering with the transcription of genetic information on the ribosomes

Rifampicin

Antimetabolite action

Sulfonamides, Sulfones, PAS, INH, Ethambutol and Trimethoprim.

SULFONAMIDES

The antimicrobial compounds containing a sulfonamido (SO_2NH_2) group are termed as sulfonamide (Fig. 40.1). The sulfonamido group is also present in other non-antibacterial compounds like the antidiabetic agent tolbutamide, diuretics like chlorothiazide and its congeners, furosemide and acetazolamide and anticonvulsants like sulthiame.

Physical and chemical properties: The sulfonamides are white crystalline powders, mildly acidic in character and relatively insoluble in water. They form salts with bases and their sodium salts are water soluble. The pH of the sodium salts, with the exception of sodium sulfacetamide and sulfasomizole however, is very high; given intramuscularly, the marked alkalinity causes damage to the tissues.

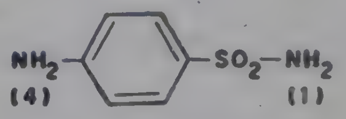

Fig. 40.1: Basic structure of a sulfonamide.
N_1—Nitrogen of the sulfonamido group.
N_4—Nitrogen of the para-amino group.

Chemically, the antibacterial activity of sulfonamides depends on:

(a) a free or potentially free para amino group. Thus sulfonamides, containing this group either intact or substituted by such radicals as can be converted into free amino group in the body show antibacterial activity, and

(b) a direct link of the sulfur atom of the sulfonamido group with the benzene ring.

Classification: The sulfonamides can be classified according to their therapeutic utility as:

I. Those employed for the treatment of systemic infections and II. Those employed for the treatment of local gastrointestinal infections.

I. Sulfonamides employed for the treatment of systemic infections are usually administered orally. Depending upon their duration of action, they can be further subdivided into:

(a) *Short acting sulfonamides*: The important compounds of this class are Sulfanilamide, Sulfadiazine, Sulfadimidine (sulfamethazine), Sulfamerazine, Sulfacetamide, Sulfafurazole (sulfisoxazole), Sulfasomidine and Sulfamethizole.

(b) *Intermediate acting sulfonamides*: Sulfamethoxazole, Sulfasymazine and Sulfaphenazole.

(c) *Long acting sulfonamides* like Sulfamethoxypyridazine, Sulfadimethoxine, Sulformethoxine.

II. Sulfonamides employed for the treatment of local gastrointestinal infections include Sulfaguanidine, Succinylsulfathiazole, Phthalylsulfathiazole and Salicylazosulfapyridine.

Mafenide hydrochloride, with a different mechanism of action is used topically.

Pharmacological actions: Their most important pharmacological action is antibacterial activity. They are effective against a variety of Gram positive and Gram negative organisms and certain chlamydia infections; these are:

(a) *Streptococci, Staphylococci* (some strains), *Gonococci, Pneumococci* and *Meningococci.*

(b) *Clostridia, Bacillus anthracis.*

(c) *Haemophilus influenzae, H. ducreyi, Vibrio comma, E. coli, Pastuerella pestis, Shigella, Donovania granulomatosis.*

(d) *Nocardia, Actinomyces* and *Toxoplasma.*

(e) Chlamydia organisms causing lymphogranuloma venereum, psittacosis and trachoma.

They are mainly bacteriostatic, but occasionally, in very high concentrations, particularly in the urinary tract, they may act as batericidal compounds. Their clinical efficacy and potency are much less than those of antibiotics. Thus, the minimum inhibitory concentration of sulfonamides for a highly susceptible bacterial strain is 1:10,000 to 1:20,000, in comparison to 1:50 million observed with penicillin.

Mechanism of action: The compound sulfanilamide exhibits a structural similarity to para amino benzoic acid (PABA) (Fig. 40.2). It has been proposed, therefore, that sulfonamides, by virtue of their structural similarity to PABA, compete with and probably substitute the latter in the bacterial metabolism (Woods-Fields theory)

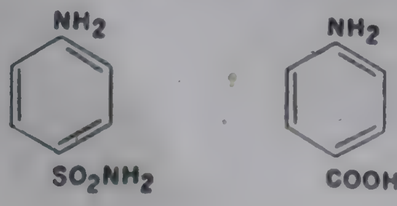

Fig. 40.2: Sulfanilamide PABA

Folic acid derived from PABA is important in bacterial metabolism. Sulfonamides inhibit the enzyme folic acid synthetase which is involved in the conversion of PABA to folic acid. This causes folic acid deficiency resulting in injury to the bacterial cell. Such an injured or disrupted bacterial cell can be easily phagocytosed.

Following observations support the Woods-Fields theory:

(i) The antibacterial activity of sulfonamides is confined only to micro-organisms which synthesize their own folic acid; they are not effective against micro-organism capable of utilizing folic acid from the environment.

(ii) Sulfonamides are ineffective in the presence of pus and tissue breakdown products which contain a large amount of PABA. Similarly, drugs which yield PABA in the body after biotransformation, e.g. procaine, amethocaine and procainamide antagonize the sulfonamide action.

(iii) The bacteriostatic action of sulfonamides can be countered by PABA, and

(iv) Sulfonamide resistant micro-organisms often show an enhanced PABA synthesis.

This theory, however, cannot explain the antibacterial action of mafenide hydrochloride. The antibacterial action of this compound is not antagonized by PABA.

Sulfonamide resistance: A variety of *micro-organisms* including *Staphylococci, Streptococci, Pneumococci, Meningococci, Gonococci* and *E. coli* can acquire resistance to sulfonamides with a consequent diminution in their therapeutic utility. Some of the resistant strains synthesize a folic acid synthetase with a lowered affinity for sulfonamide while some others overproduce p-aminobenzoic acid. There is, however, no cross resistance with the antibiotics.

Absorption, fate and excretion: Sulfonamides intended for systemic use are rapidly absorbed from the gastrointestinal tract and 70 to 90 per cent of the oral dose reaches the blood stream. The main site of absorption is the small intestine, although variable quantities are absorbed from the stomach. Among the short acting sulfonamides, sulfamerazine is more rapidly absorbed than sulfadiazine and sulfadimidine. Sulfonamides used for local action in the intestines are poorly absorbed; sulfaguanidine is absorbed to a greater extent than phthalylsulfathiazole and succinylsulfathiazole. The absorption of sulfonamides from other sites like the abraded skin, respiratory tract and vagina is variable, but sufficient amounts may be absorbed from these sites to produce sensitization and even toxicity.

In the blood, these drugs are loosely bound to plasma proteins, particularly albumin. The degree of binding differs among the various compounds. In general, at least 50 per cent of the compound is bound to plasma proteins.

Protein binding of sulfonamides is important for several reasons. The bound sulfonamide has much less of bacteriostatic activity and cannot normally pass into tissue fluids or cross the blood brain barrier. Since the bound form is not available for renal excretion, protein binding helps to prolong the action of sulfonamides. It has been claimed that in the bacterial cell, the effective concentration of the drug depends on the proportion of the free sulfonamide not combined with bacterial protein. Hence, the highly protein bound sulfonamides will not be so effective in the treatment of acute infections. The long acting sulfonamides are long acting because they are extensively bound to plasma proteins and are excreted slowly.

The free form of sulfonamides is uniformly distributed throughout all the tissue fluids although the concentration in the tissue fluids is usually lower than in the plasma. Higher CSF concentrations are achieved in the presence of meningeal inflammation.

Sulfadiazine, because of lesser degree of binding with plasma proteins, achieves a CSF concentration of 50 to 80 per cent of the plasma levels while with sulfadimidine, CSF concentration is 30 to 70 per cent. Sulfadiazine, therefore is considered superior to sulfadimidine in the treatment of meningococcal meningitis. In practice, however, adequate CSF concentration is achieved with majority of the short acting sulfonamides given orally. These drugs readily cross the placental barrier, the foetal concentrations being approximately equivalent to maternal blood levels; they are also secreted in milk.

Sulfacetamide and sulfadiazine readily penetrate into the aqueous humour.

After a single oral dose of a short acting sulfonamide, the peak plasma concentration is usually reached within 2 to 4 hours. The effective blood levels vary between 6 and 12 mg. per 100 ml. As the sulfonamides are concentrated by the kidney, lower plasma levels of sulfonamides are adequate to produce therapeutic benefits in the treatment of urinary tract infections.

The major pathway in biotransformation of sulfonamides is the acetylation of the nitrogen of the para-amino group (N 4), resulting in a loss of the antibacterial activity. Acetylation chiefly occurs in the liver. The degree of sulfonamide acetylation varies in different species and according to the preparation employed. Acetylation is totally absent in the dog. In man, sulfadiazine is much less acetylated than sulfadimidine while sulfamethoxypyridazine is acetylated to the extent of 10 to 15 per cent.

Individuals can be differentiated into two distinct groups according to their capacity to inactivate sulfonamides. '*Rapid acetylaters*' acetylate 62-90 per cent of sulfadimidine while '*slow acetylaters*' acetylate only 40-53 per cent of it. Genetically, the capacity for rapid acetylation is transmitted by a single gene.

The acetylated form, though devoid of antibacterial activity, possesses the toxic potentialities of the parent drug. In addition, certain acetylated products are poorly

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soluble in acidic urine and may cause crystalluria and renal complications. The degree of acetylation increases with prolongation of the drug sojourn in the body as in the presence of renal damage. The urinary solubility of acetylated derivatives of sulfadiazine and sulfamerazine is greatly increased in alkaline urine; the acetylated as well as the free forms of compounds like sulfacetamide, sulfafurazole, sulfasomidine and sulfamethizole are, however, soluble in an acid urine.

The free and the acetylated sulfonamides are mainly eliminated in urine, mostly by glomerular filtration and to a small extent by tubular secretion. Only the non-protein-bound form of sulfonamides is available for glomerular filtration. The urinary concentration of sulfonamides is higher than their plasma levels. These compounds undergo a variable degree of tubular reabsorption; sulfacetamide, however is not appreciably reabsorbed. Sulfafurazole and sulfasomidine are excreted more rapidly than sulfadiazine, sulfadimidine and sulfamerazine, while the excretion of the intermediate and the long acting sulfonamides is slow. These agents are also present, in small amounts, in sweat, bile, saliva and the intestinal secretions.

Adverse reactions: The originally employed sulfonamide compounds like sulfanilamide, sulfapyridine and sulfathiazole are obsolete because of their high toxicity. A variety of safer preparations is now available. *Unfortunately, there is a tendency to exaggerate the ill-effects of these drugs which are still valuable in therapeutics.* However, the toxic potential of these drugs should be remembered and their indiscriminate use avoided. The drugs commonly produce nausea and vomiting. These are rarely troublesome. In spite of their wide antibacterial range, sulfonamides do not usually produce troublesome disturbances in the gut flora unlike the broad spectrum antibiotics. The major adverse reactions include:

(a) *Intolerance*: This usually becomes apparent within 1 week or more after drug administration. The commonest allergic symptoms are drug fever, skin rash, usually morbilliform in type and eosinophilia. The rash is often accompanied by conjunctivitis. Rarely, severe exfoliative dermatitis accompanied by high fever may develop. Sulfonamide drug fever usually disappears within 72 hours of discontinuation of medication. Serum sickness, characterised by fever, joint pains, urticaria, bronchospasm and leukopenia sometimes develops within the 1st or 2nd week after commencement of therapy. Anaphylactoid reaction is rare.

The uncommon allergic manifestations include cutaneous photosensitization, a fatal necrotizing arteritis resembling polyarteritis nodosa, acute toxic hepatitis and rarely fatal hepatic necrosis, toxic nephrosis, and acute haemolytic anemia.

A severe exudative type of erythema multiforme, associated with widespread lesions of the skin and mucous membranes, termed *Stevens Johnson syndrome*, has been reported with long acting sulfonamides. The syndrome, which is common in children, is usually a self-limiting disease but occasionally can be fatal.

Sulfamethoxypyridazine may induce allergic myocarditis and a peculiar syndrome characterised by urticarial rash, bronchospasm and appearance of L.E. cells in the peripheral blood.

Cross sensitivity among various sulfonamides and between sulfonamides and other drugs containing the sulfonamide (SO_2NH_2) group such as diuretics is known. Local application of sulfonamides is discouraged as it may sensitize the patient.

(b) *Urinary tract*: In the presence of acid urine the acetylated form of the drug may be precipated, mainly in the collecting tubules and the calyces. This causes renal irritation, obstruction to the urine flow and may precipitate renal colic. Crystalluria, albuminuria and haematuria can occur, leading to the development of oliguria and anuria.

The renal complications during sulfonamide therapy can be minimised by:

(i) Ensuring an adequate output (one

itre or more) of urine.

(ii) Making the urine alkaline with the use of an alkaline mixture to increase the solubility of the conjugation product.

(iii) Using combinations containing two or three sulfonamide preparations or by using sulfonamides with high solubility or compounds like sulfafurazole and sulfasomidine, the acetylation products of which are highly soluble in urine.

(c) *Haemopoietic system*: The haemopoietic toxicity includes agranulocytosis, thrombocytopenia resulting into petechiae, hematuria and epistaxis, and rarely aplastic anemia. Sulfonamides, like many other drugs, tend to oxidize hemoglobin to methemoglobin. In patients with G6PD deficiency, these compounds may cause ntravascular hemolysis.

Sulfonamides compete with serum bilirubin for albumin binding sites. Administered during late pregnancy they may displace bilirubin from albumin binding sites in the foetus. The free bilirubin, by crossing the blood-brain barrier, which is permeable to bilirubin only in foetuses and nfants, causes kernicterus. Sulfonamides may also cause kernicterus when administered to new born and premature infants, particularly in those with G6PD deficiency. They should be avoided in infants.

As the long acting sulfonamides are extensively bound to plasma proteins, their administration is associated with a greater risk of kernicterus.

(d) *Miscellaneous*: These include cenral nervous system disturbances like confusion, depression, ataxia, tinnitus, fatigue and acute psychotic episodes. These disturbances are commoner in children than in adults. Rarely, peripheral neuritis may occur. Endocrinal disturbances such as goitre and hypothyroidism have been reported.

Sulfonamides can displace other drugs from their protein binding with resultant toxicity. Thus, warfarin given in combinaion with sulfonamide may cause a sharp ncrease in the anticoagulant effect. Sulaphenazole has been reported to produce hypoglycemia in patients on tolbutamide therapy. Jaundice due to liver damage is rare.

Preparations and dosage: A large number of sulfonamides are available for therapy. Only the compounds used commonly are described in Table 40.1.

Therapeutic uses: The therapeutic utility of a sulfonamide is determined by:

✓(i) its absorption from the gastrointestinal tract.

(ii) the degree of protein binding and concentration of free and acetylated forms in the plasma and CSF,

(iii) the rate of renal excretion, concentration and solubility of acetylated and free forms in urine.

(iv) the host resistance, presence of pus and tissue breakdown products,

(v) the type of pathogenic organism and the anti-bacterial activity of the drug,

(vi) its toxic potentialities and

(vii) the cost of therapy.

Many compounds offered in the market, however, have marginal differences. In fact, there is hardly any need for the existence of so many different compounds. In practice, one needs to remember only a few drugs from each group. For routine systemic use, sulfadimidine, sulfadiazine and similar other short acting compounds are equally good; hence, a cheaper compound should generally be preferred.

Sulfonamides are not usually recommended in infections due to staphylococci, streptococci, pneumococci and gonococci owing to a high degree of resistance in majority of the organisms and the availability of more potent and safer bactericidal agents. They are useful in the treatment of lymphogranuloma inguinale and venereum but tetracyclines are usually preferred.

As these drugs are bacteristatic, effective blood levels must be maintained by a regular dose regime.

The important therapeutic uses of sulfonamides are:

(i) **Acute bacillary dysentery:** See Chapter 44.

Table 40.2: **Sulfonamide preparations**

Name	Properties	Oral dose recommended	
		Adult	Children
SHORT ACTING			
Sulfadiazine I.P. tab. 500 mg.	Low (50%) degree of protein binding and better diffusion into C.S.F. Tendency to cause crystalluria.	Initial: 2-3 g. Then 1 g. 4-6 hourly	150 mg/kg/24 hours (4-6 doses)
Sulfadimidine I.P. tab. 500 mg.	Acetyl derivative relatively soluble in acid urine.	Initial: 2-3 g. Then 1 g. 6 hourly	
Sulfamerazine	Less potent. Usually used in combination with other sulfonamides.		
U.T.I Sulfafurazole (Sulfisoxazole, Gantrisin) tab. 500 mg.	Rapid excretion. High concentration in plasma. Less acetylated. Both free and acetylated forms soluble in urine even at acidic pH. Preferred in urinary tract infections.	Initial: 3 g. Then 1.5 g. 6 hourly	60 mg/kg. Then 30 mg/kg. 4 hourly
Acetyl sulfafurazole	Tasteless. Splits in the intestines to provide the basic drug.		Pediatric syrup and suspension 500 mg/ml
Sulfasomidine (Elkosin) tab. 500 mg.	Rapid excretion. Less acetylated. Free form highly soluble even in acidic urine. Preferred in urinary tract infections.	Initial: 3 g. Then 1.5 g. 6 hourly	Six months to years: Initial: 1 g.; then 0.25 g. 6 hourly. Three to 10 years: Initial: 1.5 g. then 0.5 g. 6 hourly
Sulfamethizole (Urolucosil) tab. 100 mg.	Rapid excretion, mostly (90%) in free form. Highly soluble even in acid urine. Preferred in urinary tract infection. The drug may form an insoluble precipitate with formaldehyde in urine and hence methenamine compounds should not be given with this agent.	0.1-0.2 4-6 hourly	30-45 mg/kg. 24 hours (4 doses)
Sulfachlorpyridazine tab. 500 mg.	Rapid excretion. Highly soluble in acid urine.	Initial: 1-3 g. Then 1 g. 4-6 hourly	
Sulfacetamide I.P. (Albucid)	Less protein-bound (15-20%). Free and acetyl forms soluble in urine. Low therapeutic activity. Sodium salt has almost neutral pH and better penetration in tissues. Used locally for eye infections.	Locally, eye ointment I.P. 6%; Eye drops N.F. 10-30%	60 mg/kg/24 hours
INTERMEDIATE ACTING			
Sulfamethoxazole (Gantanol) tab. 500 mg.	Prolonged action.	Initial: 1-2 g. Then 0.5-1 g. 12 hourly	

Table 40.2—continued

Name	Properties	Oral dose recommended	
		Adult	Children
Sulfamoxole (Sulfuno)	Prolonged action.	0.5-1 g. 12 hourly	
Sulfaphenazole (Orisul) tab. 500 mg.		Initial: 1 g. Then 0.5 g. 12 hourly	65 mg/kg followed by 30 mg/kg 12 hourly
	LONG ACTING		
Sulfadimethoxine (Madribon) tab. 500 mg.		Initial: 1 g. Then 0.5 g. every 24 hours	30 mg/kg followed by 15 mg/kg 24 hourly
Sulfamethoxypyridazin N.F. (Lederkyn, Midicel) tab. 500 mg.	Highly protein bound. Very slow excretion. Less tissue diffusion. May cause cumulative toxicity.	Same as above	
Sulformethoxine (Sulfadoxine, Fanasil)	Highly protein bound. Very long half life (150-200 hours) in body.	Single dose of 2 g. every 7 days	
	POORLY SOLUBLE, POORLY ABSORBED		
Sulfaguanidine tab. 500 mg.	Used in intestinal disinfection.	3-6 g. 6 hourly	150 mg/kg 24 hourly
Succinylsulfathiazole (Sulfasuxidine) tab. 500 mg.	Hydrolysed to sulfathiazole in the colon. Prolonged treatment impairs the synthesis of vitamin K by the intestinal flora.	10-20 g. daily in divided doses	250 mg/kg/24 hours
Phthalylsulfathiazole (Sulfathalidine) tab. 500 mg.	Same as above.	5-10 g. daily in divided doses	50-100 mg/kg every 24 hours
	MISCELLANEOUS		
Sulfasalazine (Salazopyrine) tab. 500 mg.	Combination of sulfapyridine and 5-amino salicyclic acid. Partially hydrolysed to sulfapyridine in the intestines. Effective in mild cases of ulcerative colitis.	0.5-1 g. 4-6 hourly	
Mefenide hydrochloride (Marfanil)	Soluble sulfonamide, effective in the presence of pus. Used topically, in ear, nose, throat infections. Some action against *Cl. welchii* and *P. aeruginosa*.	2-5% with 1% methyl cellulose. And as 10% cream	

Injectible preparations: Sulfadiazine sodium, 250 mg/ml. in 10 ml. Dose, adults 100 mg/kg body weight, 2 g. initially, then 30-50 mg. per kg. every 6-8 hourly. As the solution is strongly alkaline it is usually given i.v. in a concentration not exceeding 5 per cent.

(ii) Sulfafurazole diolamine solution 400 mg/ml. in 5 and 10 ml. Dose, adults same as oral dosage, given intravenously or subcutaneously.

(iii) Sulfadimidine injection 1 g. in 3 ml. for intravenous and intramuscular use. Dose 2 g. initially subsequently upto 6 g. daily in divided doses.

(ii) **Urinary tract infections:** See Chapter 46.

(iii) **Meningococcal meningitis:** The sulfonamides are useful both for treatment as well as prophylaxis in meningococcal meningitis. Sulfadiazine is usually preferred. This is discussed in Chapter 41.

(iv) **Haemophilus influenzae meningitis:** Some authorities regard sulfonamides as useful adjuncts in treating this condition. However, at present many prefer ampicillin or chloramphenicol. Combination of sulfadiazine with chloramphenicol is probably synergistic in this condition.

(v) **Chancroid:** Sulfadimidine, 1 g. 4 times daily for 7 days achieves a clinical cure in this condition.

(vi) **Trachoma and inclusion conjunctivitis:** Both orally administered sulfadiazine and topically applied sulfacetamide sodium penetrate into the aqueous humour in high concentrations. Sulfonamides relieve pain, photophobia, lacrimation and blepharospasm associated with this condition. Granulations of the palpebral conjunctiva and corneal ulcers improve and may even disappear and unpleasant sequelae like blindness are prevented. Tetracyclines are, however, better and usually preferred.

(vii) **Use in prophylaxis:** Sulfadimidine in the dose of 1 g. twice daily has been recommended to prevent attacks of streptococcal tonsillitis in patients who have recovered from rheumatic fever. As the beta-haemolytic streptococci may often be resistant to sulfonamides, their use is restricted to cases exhibiting allergy to penicillin. They can also be used in chemoprophylaxis of bacillary dysentery and meningococcal meningitis. A long acting sulfonamide like sulfamethoxypyridazine, 1.5 g. weekly, may be administered instead of daily sulfadiazine or sulfadimidine in such cases.

(viii) **Miscellaneous:** Sulfadiazine, in the dose of 4 to 6 g. daily for several months is of some value in nocardiasis. Sulfonamides are often combined with pyrimethamine in the therapy of toxoplasmosis, and of malaria. The locally acting sulfonamides are employed for intestinal sterilization prior to major bowel surgery. Their use in resistant malaria is discussed in Chapter 50.

Although sulfonamides are mainly bacteristatic, they do not antagonize the bactericidal effects of penicillin and could be combined with it for treating susceptible infection.

NITROFURANS: The antibacterial activity of the nitrofuran compounds was demonstrated by Dodd and Stillman in 1944.

Pharmacological actions: Nitrofurans exert a bacteriostatic action against a variety of Gram positive and Gram negative organisms including *Staphylococci, Streptococci, E. Coli, Salmonella* and *Shigella* organisms. Some of these compounds, particularly furazolidone, inhibit the growth of *Trichomonas vaginalis*, a protozoal organism, while another compound nifuroxime is effective against *Candida albicans* and other fungi. Though usually bacteriostatic, the nitrofurans can be bactericidal in high concentrations. The presence of heavy bacterial infection, plasma or blood reduces the antibacterial activity of these compounds. The development of bacterial resistance has been demonstrated *in vitro* and cross resistance among the various compounds is also observed.

The mechanism of antimicrobial action of nitrofurans is not clear. It has been postulated that they inhibit reversibly the anaerobic steps of pyruvate metabolism in bacteria.

Adverse reactions: These include intolerance which may manifest itself as nausea, vomiting and skin rashes of various types. Rarely, haemolytic anemia may develop in individuals with glucose-6-phosphate dehydrogenase deficiency. An anaphylactic reaction has occasionally been reported. The drug may rarely produce megaloblastic anemia due to folic acid deficiency and precipitate antabuse-like reactions in alcoholics. Polyneuritis is an important adverse effect which particularly occurs in the presence of an impaired renal function. Chronic medication can rarely cause interstitial pulmonary fibrosis. Deafness associated with tinnitus and dizziness has been reported with furazolidone. It may also increase sensitivity to exogenous catecholamines by inhibiting MAO.

Preparations:

Nitrofurans are yellow, crystalline compounds, sparingly soluble in water. The drugs available for therapy are:

I → (a) NITROFURANTOIN (Furadantin): It is rapidly and completely absorbed from the gastrointestinal tract. It does not achieve a bacteriostatic concentration in the plasma but approximately 40 per cent of the drug is excreted unchanged by the kidney, achieving a bacteriostatic concentration in urine. The plasma half life is 0.3–1 hour. The drug, effective against a variety of Gram positive and Gram negative organisms, including *E. Coli* and *Aerobacter*, is used exclusively as a urinary antiseptic. The lower plasma levels achieved by oral route make such treatment useless for systemic infections. The details are discussed in Chapter 46.

It is available as 50 mg. tablets and is administered orally in the dose of 50-150 mg six hourly. The comparable dose in children is 60 mg. up to 1 year, 75 to 100 mg. from 1 to 5 years and 150 to 200 mg. from 6 to 12 years in 3 or 4 divided doses. The drug should not be continued in this dose for more than 2 weeks. It does not appear in the urine in severe renal failure and in azotemic patients. The drug colours the urine brown.

(b) FURAZOLIDONE (Furoxone): This compound is effectively employed in the treatment of gastrointestinal and vaginal infections such as bacterial enteritis, bacillary dysentery, giardiasis and trichomonal vaginitis. The drug does not significantly depress the normal intestinal flora. It is bactericidal.

The drug is administered by mouth, the adult dose is 100 mg. 4 times daily for 5-7 days. It is used locally, along with nifuroxime, in the treatment of bacterial, trichomonal and monilial vaginitis.

(c) NIFUROXIME: The compound is effective against the fungus *Candida albicans*, a common vaginal pathogen, and is locally employed usually along with furazolidone.

(d) NITROFURAZONE (Furacin) is available as 0.2 per cent solution and ointment for topical application for the treatment of superficial wounds and skin infections. Systemic allergic reactions, however, may occur after such topical therapy. It is used systemically in trypanosomiasis. (Chapter 52.)

NALIDIXIC ACID (Neg-Gram, Gramoneg): It is a naphthiridine derivative, synthesized in 1962.

As suggested by its trade name, nalidixic acid is effective against certain Gram negative bacteria, especially *E. coli.* The most important action, however, is its efficacy against many strains of Proteus. It is effective to a less extent against Aerobacter and Klebsiella species and occasionally against pseudomonas. It is relatively ineffective against Gram positive organisms. The drug acts by interfering with the synthesis of nucleoprotein (DNA). Bacteria develop resistance to this compound fairly rapidly *in vitro*.

Despite its low solubility in water, nalidixic acid is readily absorbed from the gastrointestinal tract. The serum levels of the drug are low and a considerable quantity of the drug is bound to plasma proteins, but approximately 80 per cent of it is eliminated in urine within 8 hours. It is present in the urine in both active (20 per cent) and inactive, conjugated (glucuronide) forms. When clinical dosages are administered, the urinary concentration of the active drug (15 to 185 μg./ml.) is adequate for antibacterial action. The excretion of the free form of the drug is increased in alkaline urine. The drug does not show cumulative toxicity. Both the agent and its degradation products are soluble in urine and there is no danger of crystalluria.

The adverse reactions include nausea, vomiting and diarrhoea. Allergy is manifested by pruritus, rash, urticaria, fever, eosinophilia and photosensitivity. The central nervous system manifestations include headache, malaise, drowsiness and myalgia. Convulsions may appear with overdosage, particularly in children. There is some evidence that the drug may produce respiratory depression in cases of advanced pulmonary infection with respiratory insufficiency. Development of hemolytic anemia in a two week old baby fed on breast milk has been reported due to the presence of the drug in the breast milk.

Nalidixic acid is available as 250 and 500 mg. tablets and as syrup. The usual adult dose is 4 g daily given in 4 divided portions. (See Chapter 46.) Children may be given 55 mg. per kg. body weight per day in 2 or 4 divided doses.

The drug should not be employed in individuals with severe cerebral arteriosclerosis, parkinsonism, marked impairment of hepatic and/or renal functions and in those with a history of convulsive seizures.

TRIMETHOPRIM: This is a pyrimidine derivative which has been shown to be effective against many common pathogenic bacteria. It is slightly soluble in water. Given alone, it is bacteristatic. In *in vitro* studies it is highly effective against *Staph. aureus*, *Streptococci*, *C. diphtheriae*, *E coli*, *Salmonella*, *Shigella*, *H. influenzae*, *K. pneumoniae*, *Proteus* and *V. cholerae*. It is somewhat less effective against *N. gonorrhoeae*, *N. meningitidis*, *Cl. welchii* and *B. pertusis*. Mycobacteria and pseudomonas are not affected.

Bacteria and protozoa synthesize folic acid from para-aminobenzoic acid. Trimethoprim acts by inhibiting the enzyme dihydrofolate reductase, necessary for the conversion of dihydrofolate to tetrahydrofolic acid. It is known that the physical properties of this enzyme in the bacterial and mammalian cells differ, resulting in a greater susceptibility of the bacterial enzyme to trimethoprim. Thus, the concentration necessary to inhibit the mammalian enzyme is about 50,000 times the concentration that inhibit the bacterial enzyme. Unlike bacteria, higher animals and man utilize preformed folic or folinic acid from the diet and are relatively immune to the harmful effect of trimethoprim. Further, any depressant effect of this drug on human folate metabolism can be overcome by feeding exogenous folate.

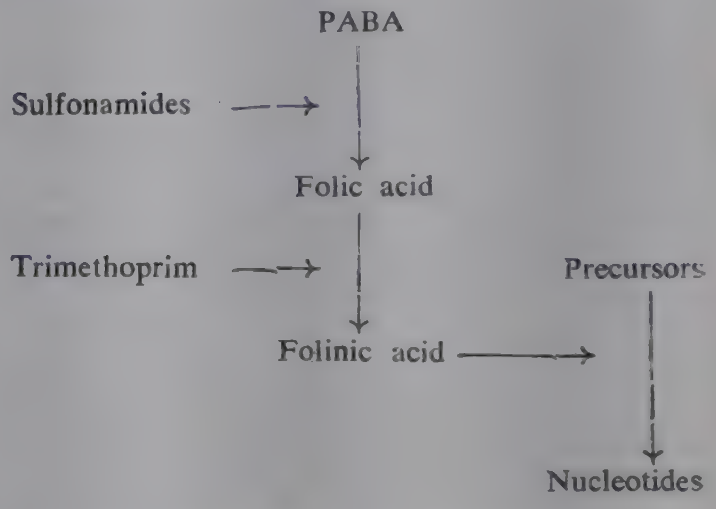

Fig. 40.3: Mode of actions of sulfonamides and trimethoprim.

It should be noted that sulfonamides act by inhibiting the incorporation of PABA into dihydrofolate by parasites. A combination of trimethoprim and sulfonamide, therefore, acts sequentially in the same metabolic pathway in the synthesis of nucleotides (Fig. 40.3). Thus, a combination of these two drugs is strongly synergistic and acts as bactericidal, whereas either drug given alone is bacteristatic. Further, bacterial resistance developes less frequently than when either drug is used alone.

Absorption, fate and excretion: Trimethoprim is rapidly and almost completely absorbed from the intestines. The peak plasma level is achieved in 1½—3½ hours.

The half lives of trimethoprim and sulfamethoxazole are 16 and 10 hours respectively. About 70% of the oral dose is excreted in the urine within 24 hours; about 80% of this is in an unchanged form. Trimethoprim is a weak base and hence, its excretion increases markedly with decrease in pH, due to ionization of the drug. The drug can also be given intravenously. Adequate concentration is reached in CSF and in bile.

Because of marked synergism between trimethoprim and sulfonamide, the drug is used in combination. To achieve optimum synergism it is combined with sulfamethoxazole which not only has absorption and excretion characteristics very close to those of trimethoprim but also has high antibacterial activity. The combination of trimethoprim 80 mg. with sulfamethoxazole 400 mg. (1:5), given orally has been shown to give the optimum synergic ratio in the plasma against common pathogens and hence, is used therapeutically.

Adverse reactions: The combination can cause nausea, vomiting and skin rashes. Glossitis and stomatitis are relatively common. Anemia, leucopenia, thrombocytopenia and even aplastic anemia have been reported. Fall in serum folate level and megaloblastic marrow changes have been observed in some cases. However, serious toxicity appears to be rare. Since, the combination contains a sulfonamide, some of the toxic effects could also be due to this component.

Preparations and dosage: (1) Co-trimoxazole is a combination of trimethoprim 80 mg. + sulfamethoxazole 400 mg. (Septran, Bactrim); dose 1-2 tablets twice daily for 10-14 days for the management of most infections. In severe infections 2 tablets thrice daily. Paediatric tablets contain Trimethoprim 20 mg. + sulfamethoxazole 100 mg. Suspension of 40 mg. Trimethoprim + 200 mg. sulfamethoxazole per 5 ml. is also available. (2) trimethoprim 80 mg. + sulfamoxole 400 mg. (Supristol).

Therapeutic uses: Although the combination is effective against many organisms, it is presently employed as the preparation of choice in the treatment of urinary infection of *E. coli* and *Proteus*. Good response has been noted in respiratory infections, gonorrhoea and typhoid fever. Since bacteria can develop resistance to this combination the drug should be used cautiously. Because of teratogenicity in animals given high doses of trimethoprim, its use in pregnancy is not presently recommended. Its use in typhoid fever and urinary infection is discussed in Chapters 44 and 46 respectively.

When creatinine clearance falls below 30 ml/ min, the interval between doses of 2 tablets should be increased from 12 to 24 hours and when it is below 15 ml/min, the drug should not be used.

41 Penicillins and Antibiotics Effective Mainly Against Gram Positive Organisms

Antibiotics are chemical substances elaborated by various species of micro-organisms, such as fungi, actinomycetes and bacteria; they suppress the growth of other micro-organisms and may ultimately destroy them. Majority of antibiotics are obtained from fungi but some like bacitracin, colistin, polymyxin B and tyrothricin are obtained from bacteria. Some antibiotics are now entirely synthesized by chemical methods e.g. chloramphenicol.

The organisms susceptible to the inhibitory or lethal effect of an antibiotic constitute its 'spectrum'. According to their spectra, antibiotics may be classified as:

I. **Antibiotics mainly effective against Gram-positive bacteria:**

(a) Those employed for systemic infections e.g. Penicillins, Erythromycin, Lincomycin, Oleandomycin, Vancomycin, Novobiocin and Fucidin.

(b) Those employed topically e.g. Bacitracin.

II. **Antibiotics mainly effective against Gram-negative bacteria:**

(a) Those used mainly for systemic infections e.g. Streptomycin, Kanamycin Gentamicin, Colistin, Polymyxin B and Cycloserine.

(b) Those used locally in the intestines e.g. Paromomycin.

III. **Antibiotics effective against both Gram-positive and Gram-negative bacteria:**

(a) Those employed for systemic infections e.g. Ampicillin, Amoxycillin, Carbanecillin, Cephalosporins, Rifamycins.

(b) Those employed topically e.g. Neomycin, Tyrothricin and Framycetin.

IV. **Antibiotics effective against both Gram-positive and Gram-negative bacteria, rickettsiae and chlamydia** e.g. Tetracyclines and Chloramphenicol.

V **Antibiotics effective against acid fast bacilli** (M. tuberculosis) e.g. Streptomycin, Cycloserine, Viomycin, Capreomycin, Kanamycin and Rifampicin.

VI. **Antibiotics effective against protozoa,** e.g. Paromomycin, Tetracyclines, Fumagillin.

VII. **Antibiotics effective against fungi** e.g. Nystatin, Amphotericin B, Griseofulvin, Hamycin, Pimaricin and Saramycetin.

VIII. **Antimalignancy antibiotics** e.g. Actinomycin D., Mitomycin and Azaserine. (See Chapter 55).

PENICILLINS

Penicillin, the most important of the antibiotics, was first extracted from the mould *Penicillium notatum*. Subsequently, a mutant of a related mould, *P. chrysogenum* was found to give the highest yield of penicillin and is now employed for commercial production of this antibiotic.

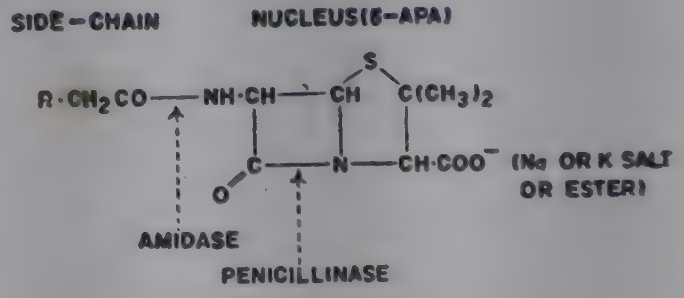

Fig. 41.1: Basic structure of penicillins.

The basic structure of the penicillins consists of a thiazolidine ring fused with a beta lactam ring. The two rings constitute the fundamental nucleus of all the penicillins, namely, 6-amino-penicillanic acid (6APA) A variety of semi-synthetic penicillins are now produced by altering the composition of the side chain attached to 6-APA nucleus (Fig. 41.1). Both the 6-APA nucleus and the side chain are essential for the antibacterial activity, but the side chain, in addition, determines stability of the penicillin against degradation by gastric acid and by the enzyme penicillinase, produced by certain micro-organisms.

The most commonly used penicillin is pencillin G or benzylpenicillin. Other forms like penicillin F, penicillin X and penicillin K are less potent, produce allergic manifestations or rapidly lead to the development of penicillin resistant bacteria.

BENZYLPENICILLIN: Benzylpenicillin is available in the form of its water soluble sodium and potassium salts. These penicillin salts in a dry state are stable at room temperature for years; the aqueous solution, however, requires refrigeration and deteriorates considerably within 72 hours.

The Oxford international unit for benzylpenicillin is equivalent to the activity contained in 0.6 micrograms of sodium salt of benzylpenicillin. 1 mg. of sodium salt is thus equivalent to 1667 units of penicillin. Commercial crystalline preparations must contain an activity not less than 1500 units per mg. of the penicillin salt. A mega unit of penicillin is equivalent to 1 million units.

Antibacterial activity: Penicillin is bioassayed by its antibacterial activity against *Bacillus subtilis* or *Carcina lutea*. Benzylpenicillin is one of the most potent antimicrobial agents and inhibits the growth of susceptible organisms *in vitro* in a concentration as low as 1 in 50 million.

Penicillin is effective mainly against Gram-positive and Gram-negative cocci and some Gram-positive bacilli. Gram-negative bacilli are usually resistant to its action. Thus, majority of *Streptococci* with the exception of D strains (enterococci) are susceptible. *Staphylococci,* initially highly sensitive to penicillin, have acquired resistance on a large scale. *Gonococci, Pneumococci* and *Meningococci* are sensitive to penicillin. *Bacillus anthracis, corynebacterium diphtheriae* and *Clostridium welchii* are moderately sensitive. Among the spirochaetes, *Treponema pallidum* is extremely sensitive to penicillin while leptospira infection responds moderately. Although penicillin is effective in actinomycosis, it is not useful in infections caused by other fungi.

Mechanism of action: Penicillin is a bactericidal drug. It is effective mainly against multiplying organisms. The lethal action of penicillin on bacteria is a slow process with a constant rate and extends over a period of many hours. The bactericidal action continues for a period of 3 to 8 hours after withdrawing penicillin G and a bacteriological cure is assured if penicillin is present in patient's plasma for a total period of 6 hours per day.

Penicillins act by interfering with the synthesis of the cell wall mucopeptide of Gram-positive cocci. This makes the cell membrane of the organism vulnerable to damage by solutes in the surrounding medium (e.g. plasma). As cell-wall synthesis occurs during the growth phase, the antibiotic is most effective against actively multiplying organisms. As penicillin does not interfere with tissue cell-wall synthesis in humans and in higher animals, it is non-toxic to them even in large doses.

The cell-walls of Gram-negative bacilli are chemically more complex. Although some inhibition of cell-wall synthesis has been demonstrated in these organisms with penicillin, a relatively high concentration of the drug is required to achieve this effect.

Absorption, fate and excretion: On oral administration, benzylpenicillin is inactivated to a significant extent by the gastric acid. The drug is mainly absorbed from the duodenum. Only a small proportion of the oral dose is detected in feces as a considerable amount is inactivated by the intestinal bacterial flora. Because of this inadequate and irregular absorption, the oral dose of benzylpenicillin required to achieve an effective therapeutic plasma level is 4 to 5 times larger than the equivalent intramuscular dose. *As food interferes with its absorption, benzylpenicillin should be given orally at least 30 minutes before, or*

2 to 3 hours after a meal. In infants, gastric acidity is lower than in adults and hence, higher blood levels are achieved relatively easily on oral administration.

Benzylpenicillin in aqueous solution is rapidly absorbed after subcutaneous or intra-muscular administration. Peak plasma level of 8 to 10 units per ml. is reached within 15 to 30 minutes and the drug disappears from the plasma within 3 to 6 hours.

As compared to plasma, penicillin levels rise slowly in the lymph but persist for a longer time. Absorption of penicillin from mucous membranes is erratic and variable. Moreover, a high risk of sensitization accompanies the use of penicillin in such forms as lozenges and troches which are, therefore, not recommended.

Penicillin is widely distributed in the body after absorption. Very high concentrations are detected in the kidneys, significant amounts are also present in plasma, liver, intestines and skin while the brain, bone marrow, skeletal and cardiac muscle contain smaller amounts. The drug penetrates poorly into the serous cavities, the concentrations in ocular, pericardial, pleural and peritoneal fluids being low. However, in the presence of inflammation, its concentration in these fluids is increased. Subconjunctival injection results in high concentration in the ocular fluid. Although normally the drug does not readily cross the blood-brain barrier, therapeutically adequate CSF concentration is achieved in the presence of meningeal inflammation. Given intrathecally, the drug persists in the CSF for 24 hours.

Penicillin traverses the placental barrier; the foetal plasma concentrations, however, are lower than the maternal plasma levels.

Approximately 60 per cent of plasma penicillin is bound to albumin; the remainder is present in the free form while traces are carried by erythrocytes; the penicillin-protein complex is rapidly dissociable. The protein bound penicillin is bacteriologically inactive.

The fate of benzylpenicillin in body is not definitely known. Nearly 30 per cent of a single parenteral dose is metabolised within the body; small amounts appear in bile, milk and saliva and the major portion is eliminated by the kidneys. About 50 per cent of the drug elimination in urine occurs within the first hour resulting in a rapid decline in the plasma level. The elimination half-time is about 30 minutes in normal adults. Nearly 80 to 85 per cent of urinary excretion occurs by tubular secretion and only 10 to 15 per cent is eliminated by glomerular filtration. Neonates and infants in whom renal function is not adequately developed, and individuals with renal insufficiency show prolonged and higher plasma penicillin levels. In anuria, the plasma half life of penicillin is increased to about 10 hours. Thus, in an adult with anuria an adequate dose for the treatment of a highly sensitive infection would be only 2000 units per dose. Probenecid, a uricosuric agent, competes with penicillin for tubular transport and can promote higher blood levels by delaying its excretion.

Approximately 20 per cent of orally administered penicillin is detected in urine, a reflection on the limited intestinal absorption of the drug.

Preparations and dosage:

(i) Benzylpenicillin (Penicillin G) I.P. The sodium and potassium salts are white, finely crystalline powders, extremely soluble in water.

Benzylpenicillin injection I.P. contains 500,000 units of the drug per ml.

(ii) Benzylpenicillin tablet B.P. contains 50,000 to 500,000 units of benzylpenicillin. Dose: 200,000 to 400,000 units 4 hourly. Peak plasma level of 0.2 to 0.3 units/ml. is reached within 1 to 2 hours after oral ingestion.

(iii) Penicillin eye ointment I.P. contains 2,000 units of benzylpenicillin per g.

Rapid urinary elimination of benzylpenicillin necessitates its parenteral administration at 4 or 6 hourly intervals, causing considerable inconvenience to the patient. Repository preparations overcome this drawback. Such preparations are relatively insoluble and hence release benzylpenicillin slowly when injected. They thus produce relatively low but prolonged concentration of the antibiotic in blood. These agents, however, are not useful for treating acute, fulminating infections where an immediate high plasma concentration of benzylpenicillin is desirable. In contrast to adults, the neonates and infants excrete penicillin slowly and hence, require 12 hourly administration of benzylpenicillin.

The commonly employed repository preparations are:

(i) Procaine benzylpenicillin injection I.P. is available in powder form, to be suspended in distilled water, prior to injection. Dose: 500,000 to 1,000,000 units daily by intramuscular injection. After administration of a single dose, the peak plasma level of 0.3 units per ml. is reached within 1 to 3 hours. This level is 25 times lower than that attained by parenteral aqueous benzylpenicillin. The drug, however, remains in blood for 8 to 12 hours, and in some patients for 24 hours. Aqueous solutions are stable for many months at temperatures below 25°C.

(ii) Fortified benzylpenicillin injection I.P. contains a mixture of procaine benzylpencillin and benzylpenicillin in the proportion of 300,000 units per ml. to 1,00,000 units per ml. respectively. Such a preparation achieves a quick and high serum penicillin concentration and the effective concentration persists in the plasma for 12 to 24 hours.

(iii) Procaine penicillin in oil with 2% aluminium monosterate (PAM): With this preparation, serum levels of penicillin are maintained for 72 hours or longer.

(iv) Benzathine penicillin I.P. (Penidure, Benapen) is a dibenzylethylenediamine salt of benzylpenicillin. It has a very poor water solubility and is administered by intramuscular injection in the dose of 300,000 to 600,000 units. With the intramuscular dose of 600,000 units, blood levels of 0.03 to 0.1 units per ml. are reached which persist for 10 days and the drug is detected in the plasma for 2 weeks. A dose of 1.2 million units produces detectable blood levels for 3 weeks.

Probenecid, when administered orally in the dose of 2 g. per day, in divided portions along with penicillin, raises its plasma level twofold to fourfold. Therapeutic plasma levels are maintained for approximately twice as long with probenecid. Probenecid is capable of producing allergic manifestations and kidney damage. The drug is not commonly used.

Adverse reactions: Penicillin is a remarkably safe drug. The only important reaction to be feared in practice is anaphylaxis.

(a) **Miscellaneous reactions:** Oral use of penicillin may rarely produce nausea and vomiting. Sterile, inflammatory reaction at the site of injection occasionally results from intramuscular administration. Following the injection of benzathine penicillin, a burning or sharp pain may occur at the site. Sometimes, aching persists for periods up to 24 hours and rarely, limping on the affected leg may occur. The local reaction may include erythema and induration; occasionally pyrexia may develop.

Prolonged administration of benzylpenicillin by intravenous route may lead to thrombophlebitis; accidental i.v. administration of procaine benzylpenicillin can cause anxiety, mental disturbances, paraesthesiae and convulsions, probably due to procaine. If the insoluble procaine particles are deposited in the lungs, they produce small pulmonary infarcts; this leads to development of dyspnoea, cyanosis, shock and occasionally death.

Benzylpenicillin, even in large doses is devoid of toxic manifestations. However, when given by intrathecal route in large doses without proper dilution, the drug may cause irritation of the central nervous system leading to convulsions, arachnoiditis and encephalopathy. Benzylpenicillin, when administered in large doses in uremic patients may achieve high plasma concentration resulting in neurotoxicity.

(b) **Intolerance:** Intolerance is a major problem with penicillin therapy and includes idiosyncratic, anaphylactic and allergic reactions. The risk of reactions is 5 to 10 per cent with benzathine penicillin, 2 to 5 per cent with procaine penicillin and 1 to 3 per cent following benzylpenicillin, when these are administered parenterally. The mortality in severe reactions has been assessed at 9 to 13 per cent. As a generalization, the incidence of these reactions is considerably greater when benzylpenicillin is used either topically or in an aerosol form, and it appears to be least when the drug is taken orally. However, fatalities have occurred following ingestion of penicillin.

Some individuals are so sensitive that the mere handling of a tablet of penicillin or just a skin test dose may cause immediate severe reaction in them. Further, severe reactions following first dose of penicillin, in persons who had never received the drug before, have been recorded. This is probably because many of us are exposed and slightly sensitized to various common air-borne moulds that readily grow on and elaborate penicillins in foodstuffs such as bread, fruit, and oil, with or without decay; many of these have penicillin-like or closely related molecules.

Present evidence indicates that the commercial penicillin may contain a powerful proteinaceous antigen with penicilloyl specificity, which can cause severe reactions in sensitive people. Since modification of penicillin may remove the proteinaceous residue, some of the semi-synthetic penicillins may be less dangerous in this respect. Alimentary digestion of this material may explain the smaller incidence of anaphylaxis on oral administration of such preparations. The semisynthetic penicillins are, however, cross allergenic in varying degrees with the natural penicillin.

The important manifestations are:

(i) *Skin rashes* of various types associated with pruritus are the most common reactions. These may appear at any time during penicillin therapy, or even 1 to 2 weeks after discontinuation of treatment. Severe reactions like exfoliative dermatitis are, however, rare.

(ii) *A serum sickness-like syndrome* characterised by rash, fever, eosinophilia lymphadenopathy, angioneurotic edema asthma and arthralgia may appear 7 to 10 days after penicillin therapy. Purpura myocarditis and hematuria develop in severe cases. Sometimes, fever with or without eosinophilia may be the only manifestation. It usually subsides 2 to 3 days after discontinuation of therapy.

(iii) *Renal disturbances* like hematuria and albuminuria are rare.

(iv) *Hemopoietic disturbances* like hemolytic anemia occur very rarely. The patients show a positive Coomb's test and serum antibodies against penicillin.

(v) *Anaphylaxis* is the most serious reaction occurring in fewer than 0.1 per cent of patients. The symptoms of anaphylaxis usually begin within a few minutes after penicillin administration. Anaphylaxis can develop even with a minute quantity of penicillin and irrespective of the route of administration. It is characterised by an acute cardiovascular collapse, bronchospasm, and angioedema, particularly edema of the larynx. This phenomenon and its treatment are discussed in detail in Chapters 1 and 20.

It is believed that penicilloic acid either alone or linked to a plasma protein is responsible for these reactions.

Tests for detection of penicillin allergy: A reliable method of detecting penicillin allergy is not yet available. History of allergy or even a positive skin test is not in itself a complete evidence of allergy, nor does a negative history or negative skin test indicate the safety of penicillin administration.

Skin tests: One method of skin testing is to scratch the skin through a drop of solution containing 10,000 units of benzylpenicillin per ml. If a central wheal due to local edema (not diffuse erythema) occurs after 15 minutes, it is considered a positive reaction.

A positive skin reaction is a relatively reliable indicator of potentially serious penicillin allergy. Unfortunately, fatal anaphylactic reactions have been reported even in persons with negative skin response, whereas some patients with a positive reaction have accepted penicillin without serious allergic reactions. Furthermore, even the small amount of penicillin used for the test may itself rarely produce severe and occasionally fatal reaction.

Another skin test involves the administration of 0.05 ml. of penicilloyl-polylysine intradermally and subsequent observation of the inflammatory response. This test is often combined with benzylpenicillin scratch test but suffers from same drawbacks as the latter.

Serological methods, such as agglutination and hemagglutination tests and the indirect basophil degranulation test are difficult, costly and unreliable.

If a person with a positive skin test has to be administered penicillin for a life-threatening infection, penicillin desensitisation should be carried out under cover of corticosteroid and antihistaminic therapy. Benzylpenicillin in the dose of 500 units should be administered initially and the dose is later increased gradually till therapeutic levels are reached. Further, corticosteroids many have to be administered in very large doses (50 to 100 mg. per day of prednisolone) to prevent the development of anaphylaxis. Such large doses of steroids may affect the host resistance and this must be weighed against the beneficial antiallergic effect desired. Serum bactericidal tests should be performed to evaluate and monitor the bactericidal regimen employed, since the clinical picture of the disease may be altered by steroids. Antihistaminics do not decrease the incidence of penicillin anaphylaxis; they are, however, valuable in controlling the commonly occurring minor allergic reactions.

(c) **Jarisch-Herxheimer reaction** is a rare reaction reported in patients with syphilis treated with penicillin. See Chapter 49.

(d) **Superinfection:** Use of penicillin may suppress the coccal members of the bacterial flora and encourage superinfection in the form of bacteremia, urinary infection or pneumonia owing to overgrowth of such resistant micro-organisms as *Klebsiella*, *Aerobacter*, *Pseudomonas* and *Candida*. This may lead to scrotal and inguinal dermatitis, and infection of the vaginal, rectal and oral mucosa by fungi.

Stomatitis, glossitis and a black hairy tongue are known to develop after local use of penicillin troches and lozenges and may occasionally occur even after systemic therapy.

(e) **Hyperkalemia:** Each 15 million units of potassium benzylpenicillin supplies 975 mg. (25 m. equiv.) of ionic potassium, and the drug, administered repeatedly in such doses to patients with impaired renal function, may cause hyperkalemia.

(f) Intramuscular aqueous procaine penicillin sometimes produces *acute non-allergic reaction*, which could be serious. It is characterized by transient palpitation, hypertension, twitchings, auditory and visual disturbances, headache, and dizziness. In addition, psychiatric symptoms like fear of imminent death and acute depersonalization may occur. The mechanism of this reaction is not clear.

Factors affecting the antibacterial activity of benzylpenicillin:

(a) *Host defence*: Penicillin, eventhough a bactericidal drug, is not able to eradicate infection if the body defence mechanisms are not fully active or are suppressed. Thus, in individuals receiving irradiation or immunosuppressant drugs or in those with agranulocytosis, penicillin, even in full therapeutic doses, may not check the infection.

(b) *Combination with other agents*: Penicillin, being a bactericidal antibiotic, should not, as a rule, be combined with bacteriostatic agents. Under certain circumstances, however, such a combination achieves better results than either of the drugs alone e.g. penicillin-sulfonamide combination in meningococcal meningitis.

(c) *Severity of infection*: Overwhelming infection and chronic infection require large doses of penicillin for eradication.

(d) *Protein binding and site of infection*: These have been discussed previously.

(e) *Bacterial resistance*: Bacterial resistance to penicillin can be natural or acquired. Fortunately, bacteria do not acquire resistance to penicillin so easily and sensitivity of most susceptible pathogens has so far remained unchanged despite its extensive use. Usually, resistance develops after very prolonged treatment and that too to a small extent. The resistance develops stepwise. Staphylococci resistant to penicillin are common. *Streptococcus viridans* also develops resistance but to a lesser extent. Partially resistant strains of gonococci and meningococci may be encountered occasionally.

Penicillin-resistant strains of staphylococci obtained from patients elaborate an enzyme penicillinase which hydrolyses penicillin to 6 aminopenicilloic acid. Staphylococci that do not produce penicillinase may, however, also develop resistance to penicillin *in vitro*. Besides penicillin resistant staphylococci, many other micro-organisms such as *E. coli*, *M. tuberculosis*, *B. anthracis* and *A. aerogenes* produce penicillinase. The enzyme is antigenic. Presence of penicillinase-elaborating bacteria in a mixed infection may lead to a rapid destruction of penicillin with a consequent reduction in its therapeutic value. Thus, penicillin may not be effective in the treatment of *Strep. pyogenes* pharyngitis if penicillinase-elaborating staphylococci are also present in the throat.

Commercial penicillinase is obtained from *Bacillus cereus*. It is employed for isolation of organisms from blood and exudates of patients receiving penicillin. It has also been administered intravenously in the dose of 80,000 units as an adjuvant to therapy of penicillin anaphylaxis to lower the plasma concentration of penicillin. However, as the effect of the enzyme is evident only after several hours, it is better suited for the treatment of reaction caused by long-acting injectable forms of benzylpenicillin. The enzyme itself may produce allergic manifestations.

Therapeutic uses:

The various regimes with benzylpenicillin, procaine benzylpenicillin and penicillin V (see later) can be summarized as follows:

Regime 1: Penicillin V 250-500 mg or benzylpenicillin 400,000—800,000 units orally every 6 hours.

Regime 2: Injection fortified benzylpenicillin (procaine benzylpenicillin 600,000 units + benzylpenicillin 200,000 units) I.M. once a day.

Regime 3: Injection benzylpenicillin 0.5 mega unit (500,000 units) I.M. every 4-6 hours (2-3 mega units per day).

Regime 4: Injection benzylpenicillin 1-2 mega units I.M. every 4-6 hours (4-12 mega units per day).

Regime 5: Injection benzylpenicillin 2 mega units I.V. every 2 hours (24 mega units per day).

They cover the methods of administration of penicillin in majority of penicillin responding infections.

Regime 1 or 2 is used in mild infection such as streptococcal pharyngitis. Regime 3 is used in a more severe infection such as uncomplicated pneumonia. Regimes 4 and 5 are needed in more severe infections such as empyema and meningitis. The choice of the regime in each individual infection is indicated below.

(a) **Pneumococcal infections:** Pneumococci are extremely susceptible to benzylpenicillin and hence, it continues to be the drug of choice for the treatment of pneumococcal infections.

(i) *Pneumococcal pneumonia*: Moderately ill patients may be treated with regime 2 and the more severely ill patients with regime 3. The treatment should be maintained until the temperature has been normal for at least 4 days. The therapeutic response becomes apparent within 48 to 72 hours and the temperature rapidly falls to normal by crisis. If there is no response within 72 hours, it is likely that the infecting organisms are other than pneumococci. The possibility of complications such as empyema, meningitis, endocarditis and pulmonary infarction should also be kept in mind. In addition, drug fever due to penicillin may cause persistence of pyrexia. In all seriously ill patients and in those with associated chronic lung infection, a combination of penicillin and streptomycin is indicated.

(ii) *Pneumococcal empyema and pericarditis:* These patients need regime 4. In addition, half to one mega unit of benzylpenicillin in 50-100 ml. of isotonic saline should be injected intrapleurally daily for several days. If the pleural fluid is thick and viscous, the proteolytic enzymes streptokinase and streptodornase should be injected intrapleurally along with penicillin, in the dose of 200,000 to 400,000 units and 50,000 to 100,000 units respectively. Several injections may be necessary, particularly when the empyema has become loculated. By the use of these enzymes combined with daily aspiration and the local injection of penicillin, prompt and permanent cure of both acute and relatively chronic empyemas has been obtained. The same regimen is also effective in pneumococcal pericarditis. When these measures do not show definite signs of being effective, surgical intervention is indicated.

(iii) *Pneumococcal meningitis* should be treated with regime 4 or 5. In addition, benzylpenicillin should also be given intrathecally, diluted with 10 ml. of saline in the dose of 30,000 units. The equivalent intrathecal dose for children is 8,000 to 10,000 units and in no case, these doses should be exceeded. Treatment is usually continued for 2 to 3 weeks. The repository penicillin preparations are of no value in the treatment of this condition. It must be emphasized that tetracyclines should never be combined with penicillin in this condition as such practice is known to increase the mortality rate.

(iv) *Other complications*: Pneumococcal bacterial endocarditis should be treated on similar lines as endocarditis due to *Str. viridans*. Other complications such as pneumococcal osteomyelitis and arthritis need regime 4 for 2 to 4 weeks. The repository preparations of benzylpenicillin should not be employed.

(b) **Streptococcal infections:**

(i) *Infections due to Strep. pyogenes* such as streptococcal pharyngitis, scarlet fever, meningitis, otitis media, mastoiditis and acute bacterial endocarditis respond satisfactorily to penicillin.

Pharyngitis and scarlet fever are treated with regime 1 or 2. Penicillin should be administered for ten days to eradicate the infection completely.

In the treatment of acute otitis media, regime 1 or 2 is used for 2 weeks. Addition of a sulfonamide is claimed to give better results. When associated mastoiditis is present, follow regime 4, for at least 2 weeks to prevent intracranial complications.

Acute bacterial endocarditis should be treated with regime 4 or 5 for at least 4 weeks. Early treatment is invaluable for reduction in mortality.

For streptococcal meningitis regime 4 or 5 is used for a minimum period of 2 weeks.

Streptococcal osteomyelitis and arthritis should be treated with regime 4. In addition, 50,000 to 100,000 units of penicillin may be instilled into the joint cavity in the presence of suppurative arthritis.

(ii) *Streptococcal subacute bacterial endocarditis.* The alpha-hemolytic streptococci (*Strep. viridans*) account for the majority of cases of subacute bacterial endocarditis while in a few cases the enterococci (*Strep. fecalis*) and coagulase negative staphylococci may be the causative organisms.

Bacterial endocarditis stands out among infectious diseases as one in which cure depends on use of drugs capable of killing bacteria in the tissues, unaided by phagocytosis or other defence mechanisms. For this reason, bacteriostatic agents like the broad spectrum antibiotics are of less value in the therapy of these conditions.

Therapeutic response in bacterial endocarditis depends upon the proper selection of antibiotics, the stage at which treatment is begun and its thoroughness. If the diagnosis and consequently the treatment are delayed, irreversible cardiac damage occurs, resulting in progressive cardiac failure. Again, the disease, once firmly established, becomes more difficult to eradicate. In all cases it is imperative that therapy be continued for a minimum period of 4-6 weeks after the temperature has become normal and monthly blood cultures be done for at least 3 months to detect a recurrence.

Before institution of therapy, isolation and identification of the causative organism are necessary. Once the therapy is started, its efficacy should be determined by a simple serum bactericidal test using the patient's own serum and own organisms. If the serum exhibits a bactericidal activity in 1:4 dilution, good correlation between therapy and cure is usually assured.

For *Streptococcus viridans* infection, 1 to 1.5 million units of benzylpenicillin are given intramuscularly at 6 hourly intervals for at least 6-8 weeks. Penicillin is needed in large doses because the protein bound fraction penetrates into the fibrin clots with difficulty. If the organisms exhibit some resistance *in vitro*, this dose is increased upto 20 million units per day and streptomycin in the dose of 1 to 2 g. is administered intramuscularly daily as an adjuvant. Probenecid, 0.5 g. 4 times a day, is also employed in such cases to retard penicillin excretion by the kidneys.

Enterococci exhibit some degree of resistance to penicillin. The amount of the drug required, therefore, may be 20 to 100 mega units daily, administered by continuous intravenous drip along with 0.5 to 1-2 g. of streptomycin intramuscularly daily, in divided doses.

If penicillin anaphylaxis complicates the viridans endocarditis, combined therapy with erythromycin and streptomycin should be employed. Cephalothin or cephaloridin may be used as alternatives. Other antibiotics used include vancomycin, gentamicin and fucidin. Endocarditis due to enterococci, if complicated by penicillin anaphylaxis, presents a difficult problem as other antibiotics like erythromycin and kanamycin are not very effective. In such cases, large doses of corticosteroids and antihistaminics have to be employed to suppress the allergic response. Endocarditis due to Gram-negative organisms is uncommon and should be treated with the appropriate antibiotics.

(c) **Staphylococcal infections:** A major therapeutic problem is the development of penicillin resistant staphylococci. It has been estimated that over 70-90 per cent of staphylococcal infections due to hospital strains and 15 to 20 per cent of those involving organisms present outside hospitals are resistant to penicillin.

Penicillin has been claimed to penetrate poorly into abscesses. Surgical treatment is indicated in such cases whenever possible. Topical application of penicillin for cutaneous infections is discouraged because of the risk of sensitization. For serious systemic staphylococcal infections, including acute osteomyelitis, benzylpenicillin is administered in the dose 6 to 20 million units daily by intramuscular injection in divided doses or continuously by intravenous infusion. For infections caused by staphylococci producing penicillinase, one of the new semisynthetic penicillins may be employed. These are discussed later.

(d) **Meningococcal infections:** Because of the isolation of sulfonamide resistant strains of meningococci and demonstration of penicillin in therapeutic concentration in the CSF of patients suffering from meningitis, penicillin is a drug of choice. However, it can be combined with sulfonamide in the treatment of this condition with some advantage.

The patient is usually given 4 g. of sulfadiazine sodium or an equivalent amount of sulfafurazole diolamine intravenously through a normal saline drip. The same drug is also given orally for maintenance in the dose of 1 g. every 4 hours. However, in the presence of vomiting or coma, the drug has to be given intravenously at 8 hourly intervals. Benzylpenicillin is administered according to regime 4 or 5. Therapy should be continued for 2 to 5 days after complete clinical recovery. Supportive measures include treatment of dehydration and shock with fluids and vasopressors, and correction of adrenal insufficiency (Waterhouse-Friderichsen syndrome), if present, with glucocorticoids.

(e) **Venereal diseases:** Penicillin is the drug of choice in the treatment of gonorrhoea and syphilis. (See Chapter 49.)

(f) **Actinomycosis:** Penicillin is the agent of choice in this condition. It should be used as per regime 3 for a minimum period of 8 weeks. A combined therapy consisting of regime 2 along with 4 g. of sulfadiazine daily has recently been recommended. Other antimicrobial agents employed include diaminodiphenyl sulfone, streptomycin, the tetracyclines and chloramphenicol.

(g) **Anthrax:** Benzylpenicillin, administered by regime 3 or 4 for 8 to 10 days, is the drug of choice in this condition. Alternative drugs include the sulfonamides, erythromycin and the tetracyclines.

(h) **Diphtheria, tetanus and gas gangrene:** Diphtheria is treated by regime 2 or 3 for 10-12 days in addition to the administration of the specific antiserum. This helps to eliminate the diphtheria bacilli from the throat, and prevents the development of the carrier state. Tetanus and gas gangrene need regime 4 for 2 weeks in addition to the specific antiserum.

(i) **Miscellaneous infections:**

(i) For the fusospirochetal diseases including gingivostomatitis (trench mouth), pharyngitis (Vincent's angina) and lung abscess, which may progress to pulmonary gangrene, parenteral benzylpenicillin is the drug of choice, given by regime 2 or 3 for trench mouth and by regime 4 for lung abscess.

(ii) *Pasturella multocida*, a member of the respiratory flora of animals, may cause various infections such as cellulitis, meningitis, osteomyelitis and pneumonia. Benzylpenicillin by regime 4 for 2 to 4 weeks is curative.

(iii) Listeriosis caused by *Listeria monocytogenes* has a propensity to occur during pregnancy; it produces only mild influenza-like maternal symptoms. The fetus, however, may be born with endocarditis, meningitis or pneumonia. The recommended dose of benzylpenicillin for the mother is 15 to 20 million units daily intramuscularly for at least 2 weeks.

(iv) Erysipeloid, caused by the Gram-positive bacillus, *Erysipelothrix insidiosa*, responds to a single injection of 1 to 2 million units of benzathine penicillin. The organism may also cause endocarditis, which is treated in a similar fashion as viridans endocarditis.

(v) Streptobacillary fever caused by *Spirillum minus* and *S. moniliformis* responds to 12 to 15 million units of intramuscular benzylpenicillin daily. The treatment has to be given for a minimum period of 2 to 4 weeks.

(j) **Penicillin prophylaxis:**

(i) **Rheumatic fever:** Benzylpenicillin is administered in the dose of 500,000 units twice daily for 10 days during an acute attack of rheumatic fever for eradication of the streptococcal throat infection. After this, it is of utmost importance to prevent recurrence of rheumatic fever by continuous penicillin prophylaxis. For this purpose intramuscular benzathine penicillin 1.2 million units every 3 weeks provides the best protection. Penicillin V may also be used in the dose of 125 mg. 12 hourly in cooperative patients. Prophylaxis in children should continue upto the age of 35 years. In patients with valvular disease, it should preferably be life long.

(ii) **Streptococcal infections:** Oral benzylpenicillin in the dose of 200,000 units twice daily for 5 days or a single injection of 600,000 units of PAM or benzathine penicillin affords satisfactory protection from repeated infections due to *Strep. pyogenes*. Penicillin is also valuable in individuals with rheumatic or congenital heart disease, who have to undergo surgical procedures like tooth extraction and cardiac catheterization. An intramuscular injection of 600,000 to 1.2 million units of procaine benzylpenicillin 2 to 3 hours before operation protects such individuals from bacteremia and subacute bacterial endocarditis. Alternatively, 1 million units of benzylpenicillin may be administered 1 hour before, immediately and 2 hours after surgery.

(iii) **Gonorrhoea and syphilis:** Discussed in Chapter 49.

(iv) **Recurrent lymphangitis:** Benzathine benzylpenicillin, 600,000 units, administered intramuscularly once a month is effective in preventing recurrent lymphangitis and consequent lymphedema in patients who have congenital abnormalities of the lymphatic system.

(v) **Agranulocytosis:** Benzylpenicillin is used prophylactically to prevent infection in cases of agranulocytosis. Penicillin is preferred to other antibiotics as it is bactericidal and does not depress the bone marrow.

SEMISYNTHETIC PENICILLINS

The major drawbacks of benzylpenicillin are:

(i) Inactivation by the gastric hydrochloric acid.

(ii) Short duration of action and poor penetration into the CSF.

(iii) Activity mainly against Gram-positive organisms.

(iv) Development of resistant staphylococci.

(v) Possibility of anaphylaxis.

Attempts, therefore, have been made to synthesize penicillins free from these drawbacks. The problem of short duration of action of benzylpenicillin has been effectively overcome by the development of repository preparations described earlier.

It was discovered that the mould of *P. chrysogenum* which produces the natural penicillins, also produces the 6-aminopenicillanic acid (6-APA) nucleus before the attachment of the side chains. This process of attachment of the naturally occurring side chains can be inhibited, and instead, various organic radicals can be substituted. Thus, a variety of semisynthetic penicillins are now produced. All these synthetic penicillins, however, are capable of producing allergic reactions similar to penicillin G.

The semisynthetic penicillins can be classified as:

I. **Acid resistant:** Potassium phenoxymethylpenicillin, potassium phenoxyethyl penicillin and propicillin.

II. **Penicillinase resistant:** These are Methicillin, Oxacillin, Cloxacillin, Dicloxacillin, Nafcillin, Flucloxacillin and Quinacillin. All except methicillin are acid resistant as well, and can be administered by mouth.

III. **Effective against Gram-positive and Gram-negative organisms:** Ampicillin, Amoxycillin and Carbenicillin.

Ampicillin and amoxycillin, in addition, are acid resistant and can be given orally.

I. Acid resistant penicillins:

POTASSIUM PHENOXYMETHYLPENICILLIN (Penicillin V): This preparation has a similar antibacterial spectrum like benzylpenicillin though the degree of sensitivity differs. However, the drug is not inactivated by the gastric acid, and presence of food within the gastrointestinal tract does not interfere with its absorption. The potassium salt is absorbed more rapidly than the free acid. On an equivalent oral dose basis, the plasma levels achieved by this compound are 4 to 5 times higher than those with benzylpenicillin. Approximately 50 to 70 per cent of the drug is bound to the plasma proteins. Nearly 25 per cent of the drug is eliminated in the urine by a similar mechanism as benzylpenicillin.

Potassium phenoxymethylpenicillin I.P. is freely soluble in water. It is available as 65 and 125 mg. tablets. 125 mg. of the drug are equivalent to 200,000 units. The drug is usually administered in the dose of 250 to 500 mg. at 4 to 8 hourly intervals.

Penicillin V may be employed in less serious infections due to pneumococci and streptococci, in conditions that have been brought under control by parenteral therapy, and in infections which require a prolonged treatment. It is much less active than benzylpenicillin against gonococci and other gram negative species and hence it is not useful for the treatment of gonorrhoea and the gram negative infections of the respiratory or urinary tract. It may be used prophylactically for similar purposes as benzylpenicillin. A dose of 250 mg. of penicillin V 4 times daily for 4 days, with sulfafurazole 26 to 30 mg. per kg. upto 2 g. maximum per day for 3 days, has been advocated for prophylaxis against meningococcal infection in contacts and in school children during an epidemic.

Penicillin V has no place in the management of severe infections and should not be used for the initial treatment of meningitis, syphilis or actinomycosis.

POTASSIUM PHENOXYETHYLPENICILLIN (Phenethicillin): is similar to phenoxymethylpenicillin, and weight for weight, there is no difference in the antibacterial effect of these two drugs. The dosage, indications and contraindications for phenethicillin are similar to those of phenoxymethylpenicillin.

Propicillin (Brocillin, Ultrapen) is similar to the other two preparations. Its binding with plasma proteins, however, is more extensive than the other two penicillins. It does not seem to have much therapeutic advantage over penicillin V.

II. Penicillinase resistant penicillins:

METHICILLIN (Staphcillin, Celbinin): This drug is employed mainly against staphylococci resistant to benzylpenicillin as it is not appreciably inactivated by the staphylococcal penicillinase. Compared to benzylpenicillin, however, it exhibits a narrow range of effectiveness and less antibacterial activity. Thus, on weight basis it is only about 1/3rd as effective as benzylpenicillin against *pneumococci, group A streptococci* and *Strep. viridans*. The drug can stimulate the production of penicillinase by the micro-organisms and hence, should not be used indiscriminately. The mechanism of penicillinase resistance of methicillin and allied drugs is not known.

Staphylococci resistant even to methicillin have been demonstrated. The mechanism of the phenomenon is not understood. Methicillin resistant staphylococci show a corresponding increase in resistance to oxacillin, cloxacillin and nafcillin.

Methicillin is acid labile and hence, has to be administered by intramuscular or intravenous route. After a single intramuscular dose, peak plasma level is observed within 30 to 60 minutes and it declines below the therapeutic range after 3 or 4 hours. The drug penetrates into the body fluids slowly; however, significant levels are observed in CSF in the presence of meningitis. Approximately 20 per cent of the drug is bound to plasma proteins.

Renal excretion of methicillin is rapid and similar to that of benzylpenicillin. The renal excretion can be delayed by using probenecid. A small portion of the drug is secreted in bile and is eliminated in feces.

The drug has all the toxic potential of penicillin G. In addition, a number of cases of bone marrow depression and a few cases of hemolytic anemia, neutropenia and granulocytopenia have been reported with methicillin. Hematuria and nephropathy have also been recorded. Thrombophlebitis may occur on intravenous administration. Fulminating superinfection with Gram-negative organisms may occur during methicillin therapy.

Methicillin is used as the sodium salt. According to the severity of infection, the intramuscular adult dose varies from 1 to 2 g. every 2 to 6 hours. As much as 12 to 18 g may be given daily in severe cases. Children and infants are given 25 mg. per kg. 6 hourly. One to 2 g. of the drug may be administered intravenously in adults, dissolved in 30 to 50 ml. of normal saline injection, at the rate of 10 ml. per minute, every 4 to 6 hours. Since the drug is extremely unstable in acid solution and is destroyed in solution containing certain basic antibiotics like kanamycin, solutions of methicillin for parenteral use should have a neutral pH and no other drugs should be added. Dextrose solutions particularly with a pH below 5.5 should not be used to reconstitute sodium methicillin. The drug has been administered intra-articularly and intrapleurally in the dose of 0.5 to 1 g. in 5 to 10 ml. of normal saline. 500 mg. of the drug can be dissolved in about 3 ml. of distilled water and inhaled over a period of 20 minutes, 4 times daily, in the form of an aerosol, to combat resistant pulmonary staphylococcal infection.

Methicillin has been successfully used in treating meningitis, subacute bacterial endocarditis, osteomyelitis and enterocolitis due to penicillinase producing staphylococci. Because of its lower antibacterial activity the drug should not be used as substitute against organisms sensitive to benzylpenicillin.

CLOXACILLIN (Klox): This drug has a weaker antibacterial activity than benzylpenicillin but is 5 to 10 times more active than methicillin, and about twice as active as the previously introduced drug oxacillin. Although food interferes with the absorption of the orally administered drug, serum levels after oral administration of cloxacillin are higher and more predictable than after oxacillin. In some subjects, however, orally administered cloxacillin may be absorbed only to a limited extent.

After a single oral dose, peak plasma levels are attained within an hour and persist for 4 to 6 hours. The drug is distributed throughout the body, but the highest concentrations occur in the kidney and liver; approximately 90 to 95 per cent is bound with the plasma proteins. Nearly 30 per cent of a single dose is excreted in the urine, over 95 per cent of the 24 hour urinary excretion occurs within the first 6 hours. Significant amounts are excreted in the bile.

The drug is devoid of serious toxicity except the allergic reactions.

The initial oral dose of cloxacillin varies from 0.5 to 1 g. 4 to 6 hourly and the maintenance dose is 250 mg. given at the same intervals. In children, the dose varies from 50 to 100 mg. per kg. daily divided into 6 portions, according to severity of infection. The drug should be administered 1 hour before or 2 hours following a meal to ensure better absorption. It can also be given intramuscularly.

Cloxacillin and methicillin exhibit cross-resistance.

DICLOXACILLIN: This agent, a derivative of cloxacillin, has been demonstrated to give blood levels twice those of cloxacillin on oral administration. This is because it is better absorbed and slowly excreted. It is, however, very highly (95%) protein bound and does not cross the placenta significantly. It has similar properties as cloxacillin. It is administered orally or intravenously in the dose of 0.25 to 1 g. at 2 to 6 hourly intervals. About 65-75 per cent of the oral dose is excreted in the urine within 24 hours.

Flucloxacillin is similar to cloxacillin but is absorbed better.

Quinacillin is highly resistant to penicillinase and not highly protein bound. However, its oral absorption is poor.

NAFCILLIN (Unipen): In *in vitro* studies this drug has been shown to be more active than methicillin and oxacillin, but less active than benzylpenicillin against susceptible organisms. On oral administration, its absorption is slower, irregular and incomplete. Intramuscular injection yields quicker and higher plasma levels. Approximately 90 per cent of the drug is bound with plasma proteins and is mainly excreted in bile.

About 5 to 10 per cent of the oral dose and 30 to 50 per cent of the intramuscular dose are excreted in urine within 12 hours. Its toxicity is similar to that of cloxacillin.

The parenteral route is usually preferred to the oral route. The oral doses are similar to those of cloxacillin. The intramuscular dose is 0.5 to 1 g. 4 to 6 hourly and 25 mg. per kg. twice daily, respectively, in adults and in children. It can be given intravenously.

III. Effective against Gram-positive and Gram-negative organisms:

AMPICILLIN (Roscillin, Ampillin):

The antibacterial activity of ampicillin is generally the same as that of benzylpenicillin, but it is more effective than benzylpenicillin against a variety of Gram-negative bacteria. The Gram-positive cocci are slightly less sensitive to ampicillin than to benzylpenicillin. The drug is effective against. *H. influenzae*, *Strept. viridans*, *Proteus mirabilis*, *Neisseria gonorrhoea*, *Salmonella typhosa*, many strains of *E. coli* and several strains of *Shigellae*. The drug is moderately effective against *Klebsiella*, certain strains of *Aerobacter* and *Enterococci*. The *Pseudomonas* and indole positive *proteus*, however, are resistant to this drug. Enteric bacilli, especially *E. coli* and *Proteus*, can develop resistance to ampicillin. Ampicillin is inactivated by penicillinase and, therefore, is ineffective against staphylococci resistant to benzylpenicillin. Bacteria can develop resistance to ampicillin and many strains of salmonella, shigella, E. Coli and proteus resistant to this drug have now been isolated.

Ampicillin is water soluble and acid resistant. It is readily absorbed on oral administration. Food does not significantly interfere with its absorption. The portion not absorbed is inactivated by penicillinase of the colonic bacterial flora and hence, the drug rarely produces troublesome superinfection in contrast to tetracyclines.

Peak plasma levels are reached within 2 hours and 1 hour respectively after administration of a single oral or intramuscular dose. The levels are considerably higher and more prolonged on intramuscular administration. The drug persists in the plasma for 6 to 8 hours, and only 20 per cent of it is bound with plasma proteins. It is excreted unchanged in urine and high concentrations are also present in the bile. Tubular excretion is less pronounced than with penicillin G. In premature and very young infants, excretion of ampicillin is delayed. The drug crosses the placental barrier and achieves therapeutic concentrations in the amniotic fluid.

The adverse effects are similar to those of penicillin G, skin rashes being more common.

The usual adult dose of ampicillin by all routes is 250 to 500 mg. 6 hourly; doses as large as 1 g. may be required for more refractory Gram-negative infections. In children below 13 years, the daily oral dose of the drug is 50 to 200 mg. per kg. while parenterally, 25 to 50 mg. per kg. may be given in divided doses. High doses are used in the treatment of meningitis and bacterial endocarditis. Stability of sodium ampicillin in solution decreases markedly with increase in its concentration and storing of solutions even at refrigeration temperature results in deterioration of activity. The presence of dextrose and lactate may further accelerate the loss of potency. 500 mg. of ampicillin dissolved in 5 to 10 ml. normal saline may be injected intrapleurally or intra-articularly.

Therapeutic uses:

(i) **Urinary tract infections** caused by *E. coli*, *P. mirabilis*, non-hemolytic *streptococci* and *enterococci*. It is also useful for prophylaxis against recurrent urinary tract infection. (See Chapter 46.)

(ii) **Respiratory tract infections:** Particularly in mixed infections with *H. influenzae* and *D. pneumoniae*.

(iii) **Meningitis and subacute bacterial endocarditis:** Ampicillin, in the dose of 6 to 12 g. per day, is effective in the treatment of influenzal, meningococcal and pneumococcal meningitis. Meningitis due to *Listeria monocytogenes* responds to a dose of 2 to 3 g. per day. In children, a dose of 150 to 200 mg. per kg. is advocated. For neonatal meningitis which is commonly caused by *E. coli*, but also occasionally by Gram-positive organisms, combined therapy consisting of 150 mg. per kg. ampicillin with 15 mg per kg. kanamycin is advocated till the organisms have been identified and appropriate sensitivity tests to antibiotics are carried out. Ampicillin can also be given intrathecally in the total daily dose of 10-40 mg. in adults and 3-5 mg. in children.

Enterococcal endocarditis and bacteremia caused by *E. coli* and *P. mirabilis* have been treated with large doses of ampicillin. In the former condition, ampicillin may approach the efficacy of combined benzylpenicillin and streptomycin therapy.

(iv) **Biliary tract and intestinal infections:** Ampicillin can be used against intestinal infections due to *E. coli, enterococci, salmonella* and *shigella*. Although the drug is effective in typhoid fever, chloramphenicol appears to be superior and hence preferred. It is claimed that the relapse rate after ampicillin is low. The drug has been used to treat the typhoid carriers. Fecal or urinary excretors of salmonella organisms respond better to ampicillin therapy than biliary excretors. Good results have been obtained in shigella dysentery.

(v) **Miscellaneous:** Ampicillin might be preferred to tetracyclines in pregnant women and in infants to avoid tetracycline deposition in bones and teeth. It has also been recommended as an alternative to tetracyclines in the management of intestinal malabsorption and is preferred in the treatment of whooping cough. Granuloma inguinale responds to prolonged ampicillin therapy.

TALAMPICILLIN: This is a carboxylic ester of ampicillin. It is rapidly absorbed from the gut and is hydrolyzed by tissue esterases in the intestinal wall to release ampicillin into the circulation. It has no intrinsic antibacterial activity and hence is not likely to have direct effect on the bacterial flora of the gut. It is given in the dose of 250-500 mg 3-4 times a day.

AMOXYCILLIN (*d*-amino-p-hydroxybenzylpenicillin) is a new semisynthetic penicillin with a broad spectrum of antibacterial activity similar to that of ampicillin. It is effective on oral administration and the blood levels are twice as high as those after similar doses of ampicillin. Its absorption is not greatly influenced by food. It is not highly protein bound and the urinary excretion is higher than that of ampicillin. It is available as 250 mg. capsules.

CARBENICILLIN: This penicillin has a similar spectrum as but weaker antibacterial activity than ampicillin. Its important advantage over ampicillin is that it is effective against all strains of *proteus* and *pseudomonas aeruginosa*. It is inactivated by penicillinase.

Carbenicillin is acid labile and has to be administered by parenteral route. When given intramuscularly, the peak plasma levels are reached within 2 hours and the drug is eliminated in urine within 6 hours. Approximately 47 per cent of the drug is bound to plasma proteins.

Carbenicillin has been advocated in the dose of 1 g. 6 hourly by intramuscular injection for the treatment of urinary tract infections due to susceptible bacteria. The drug has been administered in the treatment of septicemia and chronic urinary tract infection due to *Pseudomonas aeruginosa* (*Bacillus pyocyaneus*), in the dose of 1 g. intravenously every 1 hourly, sometimes with probenecid by mouth or in combination with gentamicin. Superinfection with *Aerobacter aeroginosa* may occur with carbenicillin therapy. It interferes with platelet aggregation and may cause excessive surgical bleeding.

CARFECILLIN, a new derivative of carbenicillin, on oral administration, is rapidly absorbed and hydrolyzed to carbenicillin. Hence, it can be given orally.

ERYTHROMYCIN GROUP

Erythromycin, oleandomycin, triacetyloleandomycin and spiramycin constitute the macrolide group of antibiotics so named because of the presence of a large lactone ring in their chemical structure. All these drugs have similar antibacterial actions, erythromycin being the most effective of all.

ERYTHROMYCIN is a fermentation

product of the fungus *Streptomyces erythreus*. Its antibacterial spectrum resembles that of penicillin. Depending upon its concentration, the antibiotic can be bacteriostatic or bactericidal. It is mainly effective against the Gram-positive cocci including the *streptococci*, *staphylococci* and *pneumococci*. *Neisseria*, some strains of *H. influenzae*, *C. diphtheriae*, *Listeria Past, multocida*, *Rickettsiae* and *Treponemas* are also inhibited in low concentrations. The drug is effective against penicillin resistant staphylococci. It probably acts by inhibiting the protein synthesis by the bacterial ribosomes. Staphylococci can develop resistance to erythromycin; the mechanism is not known.

Absorption, fate and excretion: Erythromycin is mainly absorbed from the small intestine. The drug is partially destroyed by the gastric juice and, therefore, has to be administered in the form of enteric coated tablets. The ester form, erythromycin estolate, is more resistant to inactivation by the gastric acid and is better absorbed giving higher and more prolonged blood levels than the base.

Peak plasma levels are reached within 2 to 4 hours after administration of a single oral dose and the levels decline within 6 to 8 hours; hence, a 6 hourly interval is usually advocated for maintaining the blood levels. Erythromycin readily diffuses into the body fluids producing concentrations higher than the plasma levels. Penetration into the CSF is poor but in the presence of meningeal inflammation, adequate CSF concentration is usually achieved. The drug can pass into the foetal circulation.

About 2 to 5 per cent of the orally administered drug is detected in urine in the active form. The drug is concentrated in the liver and the levels of the active form in bile are significantly high. Most of the drug is metabolized in the body.

Adverse reactions: Serious untoward effects are uncommon. Allergic reactions include fever, eosinophilia, urticaria, dermatitis and lymphadenopathy. Anaphylaxis may occur rarely with the erythromycin base. Nausea, vomiting and epigastric pain have been reported with doses exceeding 1 g. and erythromycin propionate treated patients may develop acute abdominal pain mimicking biliary colic without any signs of hepatic dysfunction. Hepatic dysfunction, particularly cholestatic hepatitis and jaundice, has been described after administration of erythromycin estolate. It is probably an allergic manifestation though a direct hepatotoxic action cannot be ruled out. It usually clears up within a few days after discontinuation of therapy. Hepatic damage is a relative contraindication for erythromycin therapy.

Since erythromycin causes inhibition of the Gram-positive bacterial flora of the intestine, superinfection with Gram-negative organisms and Candida may develop.

Preparations and dosage: Erythromycin I.P. is available as enteric coated tablets containing 250 mg. of the base. Dose: 1 to 2 g. per day in divided portions, administered at 6 hourly intervals. Food should not be given immediately after administration of the base. The dose in children is 5 mg. per kg. 6 hourly in children below 1 year, 10 mg. per kg. 6 hourly in children upto 8 years and 15 mg. per kg. in children between 8 and 12 years.

Erythromycin estolate (E-mycin, Althrocin) available as tablets containing 125 and 250 mg. of erythromycin base. It is administered in similar dosage. It is tasteless and resistant to gastric acid. However, because of its hepatotoxicity, it should not be used for prolonged periods. Food does not interfere with its absorption.

Erythromycin stearate (Erythrocin), filmtabs, containing 100 and 250 mg. of the base; cherry flavoured granules for syrup containing 100 mg. per 5 ml. for children. Dose in children: 30-50 mg/kg. per day in divided doses.

Erythromycin ethylsuccinate for intramuscular injection is available as 2 ml. ampoules containing 100 mg. of the base.

Erythromycin glucoheptonate and erythromycin lactobionate are available for parenteral therapy. The intramuscular route is painful but the compounds may be administered intravenously in the dose of 1 g. at 4 to 6 hourly intervals for treating severe infections.

Therapeutic uses: Erythromycin is an effective substitute for penicillin in the treatment of a variety of infections caused by penicillin sensitive organisms. Its antibacterial activity, however, is weak as compared to that of benzylpenicillin. It is particularly valuable in patients who are sensitive to penicillins and in those where micro-organisms have developed resistance to penicillin. For subacute bacterial endocarditis due to *Strep. viridans* in a penicillin sensitive individual, 1 g. of the drug is administered at 4 to 6 hourly intervals for 4 to 6 weeks along with 0.5 g. of streptomycin intramuscularly every 8 to 12 hours. The drug eradicates the diphtheria bacillus carrier state, the dosage employed being 250 and 500 mg. every 6 hours for 10-12 days in children and adults respectively. The drug can be used for prophylaxis against streptococcal infection and rheumatic fever in the dose of 250 mg. 6 hourly.

OLEANDOMYCIN, AND TRIACETYLOLEANDOMYCIN (TAO): Oleandomycin antibiotic is obtained from the fungus *Streptomyces antibioticus* while triacetyloleandomycin is a semisynthetic derivative of the former. The antibacterial activity of these antibiotics resembles that of erythromycin. However, weight for weight, these antibiotics are far less potent than erythromycin. Besides allergic reactions, these drugs can cause hepatotoxicity. Micro-organisms rapidly develop resistance to these drugs.

As these are weak antibiotics and as the organisms resistant to these drugs show cross resistance to erythromycin, these drugs should never be employed as primary therapy. There are no rational indications even for their use in combinations with other antibiotics.

SPIRAMYCIN (Rovamycin): This is another macrolide antibiotic derived from *Streptomyces ambofaciens*, with a spectrum similar to that of erythromycin, though it is therapeutically weaker in action. It is claimed to remain in the tissues longer than erythromycin. The drug offers hardly any advantage over erythromycin. It is supplied as 250 mg. capsules. Dose 1 g. thrice daily.

LINCOMYCIN (Lincocin): Lincomycin, a monobasic compound elaborated by *Streptomyces lincolenesis*, is an orally effective antibiotic.

Lincomycin is mainly bacteriostatic and has a spectrum of activity similar to that of penicillin and erythromycin. It inhibits the growth of many Gram-positive organisms, especially *Staphylococci* (including those producing penicillinase), *Pneumococci*, certain *Streptococci* and *C. diphtheriae*. *B. anthracis* is moderately sensitive while *enterococci*, *meningococci* and *gonococci* are little affected. Development of resistance by staphylococci to this antibiotic has been reported. Like erythromycin, the drug probably acts by interfering with protein synthesis. Cross resistance with macrolide antibiotics may occur.

Absorption, fate and excretion: On oral administration, approximately 20 to 35 per cent of lincomycin is absorbed. A single oral dose of 500 mg. produces peak plasma level within 2-4 hours and minimal inhibitory concentration for many Gram-positive organisms persists for about 6 hours. Serum levels are low when the drug is taken with food. Intramuscular injection of 600 mg. of the drug produces peak plasma levels within 30 to 60 minutes, which are twice as high as those obtained on oral administration; detectable antibacterial activity persists in the plasma for 24 hours. After intravenous administration, inhibitory serum levels may persist for 12 hours.

After absorption, the drug is distributed throughout the body. Therapeutically adequate amounts cross the blood brain barrier in the presence of meningeal inflammation but not in healthy human volunteers. The drug is concentrated in the liver, spleen, kidneys and lung.

Nearly 4 to 13 per cent of the orally administered and 17 to 47 per cent of the intramuscularly administered lincomycin is excreted in the urine within 24 hours. Most of the drug is metabolized in the body. As with erythromycin, high concentration occurs in bile.

Adverse reactions: The drug is free from serious adverse effects. Nausea, vomiting, abdominal pain and diarrhoea may occur in about 20 per cent of the cases. These are usually mild and easily controlled. A few patients may experience dizziness, headache, rash, bodyache, pruritus, proctitis and vaginitis. A few instances of jaundice, leucopenia or neutropenia have been reported but these are reversible. Monilial superinfection may occur during therapy.

Preparations and dosage: The oral adult dose of lincomycin hydrochloride monohydrate is 500 mg. 3 to 4 times a daily. Children are given 30 to 60 mg. per kg daily in 3-4 divided doses. The intramuscular and the intravenous doses are 600 mg. given at 12 and 8 to 12 hourly intervals respectively. The comparative doses in children are 10 mg. per kg. and 10 to 20 mg. per kg. respectively.

Therapeutic uses: Lincomycin has been employed clinically in staphylococcal, pneumococcal and streptococcal infections not responding to penicillin or erythromycin and in individuals allergic to these antibiotics. The drug is claimed to be more effective in the treatment of chronic staphylococcal osteomyelitis probably because of its better penetration into bones.

The frequency of existing and induced resistance to this antibiotic makes it imperative that it should not be employed in conditions for which a number of other therapeutic alternatives exists.

CLINDAMYCIN (Clinimycin): This is 7-chloro-7-deoxylincomycin, a semisynthetic derivative of lincomycin. It is bacteriostatic at low concentrations and bactericidal at slightly higher ones. It has antibacterial spectrum similar to that of lincomycin. However, it is much better absorbed orally and the absorption is not significantly affected by food. About 60% of the drug and its metabolites can be recovered from faeces in animals, and 12% of the activity appears in the urine in 24 hours. The degree of protein binding is probably low. Like lincomycin, it also gives high levels in bone and in CSF in meningitis. Blood levels are not affected by hemodialysis and anuria increases the blood level only slightly. It, however, should be used with caution in liver disease. The toxicity is similar to that of lincomycin and is usually mild. Rarely it may cause nonstaphylococcal pseudomembranous colitis.

This drug, being superior, is usually employed as a substitute for lincomycin in the treatment of infections due to Gram-positive organisms. Its usual dose varies between 150-450 mg. four times daily depending upon the severity of the disease. In children and infants it is given orally in the dose of 10-20 mg./kg. daily in 3 to 4 divided doses. Intramuscularly or by i.v. infusion dose is 600 mg. 8-12 hourly. For severe infections in adults doses upto 4.8 g. i.v. infusion have been used.

VANCOMYCIN: Vancomycin, obtained from the fungus *Streptomyces orientalis*, is highly effective against Gram-positive cocci. The drug is bactericidal.

Vancomycin is not absorbed orally and intramuscular administration is very painful. The drug is given intravenously in the dose of 2 g. daily, in divided doses. Approximately 80 per cent of the drug is eliminated in urine within 24 hours.

The adverse effects of this antibiotic include local thrombophlebitis, allergic reactions and impairment of hearing. As the drug is mainly eliminated by the kidney, it should be used with caution in patients who have renal damage. Twice-weekly determinations of blood urea nitrogen are suggested for all patients receiving doses greater than 2 g. per day.

Vancomycin may be used in penicillin and cephalosporin resistant infections.

Vancomycin, when given orally in the dose of 2 to 3 g. daily in 4 to 6 divided portions, adequately controls resistant Staphylococcal enterocolitis.

NOVOBIOCIN: This antibiotic, elaborated by *Streptomyces niveus*, has similar antibacterial activity as erythromycin and penicillin. It is, however not affected by penicillinase. It is a bacteriostatic drug.

The relatively high incidence of toxic reactions prevents the routine use of novobiocin. These include gastrointestinal disturbances, dermatitis, drug fever, leukopenia and rarely, depression of the bone marrow, intestinal haemorrhages and hemolytic anaemia. In infants, it may displace bilirubin from binding with plasma proteins, and precipitate kernicterus. Superinfection by yeasts and fungi may occur. The usual oral dose of the drug is 0.5 to 1 g. at 8-12 hourly interval. Children are usually given 30 mg. per kg. per day in divided doses.

Due to the high incidence of adverse effects, the use of this drug is restricted only to staphylococcal infections resistant to other antibiotics.

FUCIDIN: Fucidin, the sodium salt of fucidic acid is obtained from the parasitic fungus *Fusidium coccineum*. It has a steroidal structure but is devoid of hormonal effects.

The drug is mainly effective against Gram-positive organisms though streptococci and pneumococci are relatively resistant. The antibiotic exerts a synergistic effect when administered in combination with penicillin and erythromycin. Staphylococci rapidly develop resistance to this antibiotic *in vitro*.

After an oral dose of 500 mg., peak plasma levels are obtained after 2 hours and antibacterial activity can be detected in the plasma upto 24 hours. Milk considerably retards the gastrointestinal absorption of the antibiotic. Very little fucidin is excreted in urine; significant amounts are present in bile.

Adverse reactions to fucidin include skin reactions, nausea, vomiting epigastric pain, diarrhoea and hepatic dysfunction. The drug may aggravate peptic ulcer and exert a catabolic effect.

In resistant staphylococcal infections, fucidin may be administered orally in the dose of 500 mg. 3 times a day. The drug depresses the production of penicillinase by staphylococci and hence, is also used as a research tool. Usually, it is employed locally as 2% sodium fucidate in a neutral ointment base.

BACITRACIN: Bacitracin is a polypeptide antibiotic obtained from *Bacillus subtilis*. It resembles penicillin in antibacterial activity. It is effective against Gram-positive organisms like *streptococci staphylococci*, *pneumococci* and *enterococci*. *Corynebacterium*, *gonococci*, *meningococci*, *Cl. tetani*, *treponema* and *H. influenzae* are highly sensitive while the actinomyces are affected only with a higher dose. Microorganisms do not readily develop resistance to bacitracin. It probably acts by inhibiting the bacterial cell wall synthesis.

Bacitracin is not much absorbed orally. Given parenterally, it is very toxic. Adverse effects include pain at the site of injection and marked nephrotoxicity. Acute tubular necrosis and anuria may occur. Allergic manifestations on topical use are uncommon. Oral bacitracin therapy may occasionally produce nausea, vomiting and abdominal pain. The drug is not used for any systemic condition. It is mainly used as an intestinal antiseptic and for topical applications in the form of powder or ointment. For intestinal use, it is given in the dose of 400,000 to 800,000 units daily in divided doses. The drug may be inhaled in the form of an aerosol mist in pulmonary diseases. A 500 units per ml. solution is employed for intrapleural and intraperitoneal instillation.

42 Aminoglycosides and Antibiotics Effective Mainly Against Gram Negative Organisms

The important group of antibiotics used mainly to treat Gram negative infections is the aminoglycosides. It includes streptomycin. kanamycin, gentamicin, tobramycin, amikacin, neomycin, framycetin and paramomycin. The aminoglycosides have certain features in common:

(1) Chemically, they contain amino sugars in glycosidic linkage.

(2) None is adequately absorbed orally and penetration into CSF is poor.

(3) They are excreted mostly by the kidneys by glomerular filtration.

(4) Bacteria develop resistance fairly rapidly to their action and may even exhibit cross resistance.

(5) They all have similar spectra of toxicity which includes ototoxicity and nephrotoxicity and

(6) They are highly effective in infections caused by Gram negative bacteria.

STREPTOMYCIN: This antibiotic obtained from *Streptomyces griseus*, is an organic base which forms water soluble salts. The base and the salts in a dry state are stable at room temperature. The aqueous solution of the salt retains its activity at pH 3 to 7 for 3 months, if kept at 28°C or below. Dihydrostreptomycin, a related compound is more stable than streptomycin, but because of its propensity to produce irreversible auditory damage, it is not commonly used in therapeutics.

Antibacterial activity: The organisms usually sensitive to streptomycin are *M. tuberculosis, Shigella* species, *E. coli, Proteus, Pseudomonas aeruginosa, Aerobacter aerogenes, H. influenzae, H. ducreyii, P. pestis, P. tularensis, Brucella, Actinobacillus mallei, Listeria* and *Nocardia.* The moderately sensitive organisms include *staphylococci, Strep. pyogens, Strep. faecalis, Strep. Viridans, D. pneumoniae, Vibrio comma* and the *Salmonella* organisms. The *Gonococci* and *Meningococci* usually exhibit a variable response.

The drug is more effective at alkaline (7.8) than acidic pH and the antibacterial activity is somewhat reduced in the presence of blood, serum and CSF. Streptomycin is bacteriostatic in low and bactericidal in high concentrations. Its bactericidal action, unlike that of penicillin, increases progressively with rise in concentration. High concentrations can be readily achieved with therapeutic doses.

Mechanism of action: The ribosomes are entrusted with the function of manufacturing enzymes under the directions from messenger R.N.A. (mRNA). It has been postulated that streptomycin combines with the bacterial ribosomes and interferes with the mRNA-ribosome combination. According to another hypothesis, streptomycin induces the ribosomes to manufacture peptide chains with wrong amino acids which ultimately destroy the bacterial cell. In streptomycin resistant organisms, the drug fails to enter the bacterial cell or the peptide chain synthesis by ribosomes continues unimpaired even in its presence. In addition, a variety of enzymes like xanthine oxidase and others involved in the Kreb's cycle are inhibited by streptomycin. This effect probably contributes to, but is not essential, for the bactericidal action of streptomycin.

Streptomycin resistance: The microorganisms readily develop resistance to streptomycin. Some important examples are *D. pneumonia, M. tuberculosis, proteus, E. coli, Aerobacter, H. influenzae, Brucella,* *Staph. aureus and Strep. fecalis*. Exposure of the micro-organisms to sub-inhibitory concentrations of streptomycin encourages the development of resistance. Streptomycin resistance is usually permanent and cross-resistance with dihydrostreptomycin is seen. Resistance appears to arise from several discrete mechanisms. It is postulated that bacterial strains genetically resistant to streptomycin multiply with elimination of sensitive bacterial strains leading to streptomycin resistant bacterial population. Some of the resistant organisms, particularly *E. coli, Brucella* and *M. tuberculosis* may use streptomycin as a nutrient. There is partial cross resistance between streptomycin and neomycin, kanamycin and paramomycin.

Absorption, fate and excretion: As streptomycin is poorly absorbed from the gut and is not inactivated there, it can be used as an intestinal antiseptic. However, because of rapid development of resistant organisms, it is not the antibiotic of choice for this purpose.

On intramuscular administration of a therapeutic dose, peak plasma level is reached within 30 to 60 minutes and antibacterial activity persists in the plasma for 6 to 8 hours. The drug is well absorbed when instilled intrapleurally. The drug is distributed extracellularly and does not readily penetrate into cells. It diffuses into the synovial, pericardial and peritoneal fluids but repeated systemic administration is necessary to produce a high concentration in the pleural fluid. It does not readily cross the blood-brain barrier; however, in the presence of meningeal inflammation, higher CSF concentrations are usually achieved. It is concentrated mainly in kidneys, liver and skeletal muscles. It crosses the placental barrier and the cord blood concentration of the drug is similar to that of the maternal blood. About 30 to 35 per cent of the drug is bound to plasma proteins.

Streptomycin is mainly excreted by glomerular filtration; a part is metabolised in the body and a small portion appears in the bile. Approximately 50 to 60 per cent of the drug is eliminated in urine in an active form within 24 hours. It can, therefore, be used in the treatment of urinary tract infections. Renal impairment retards its excretion and may cause cumulative toxicity.

The pathway of metabolic degradation of streptomycin is not known but individual variations in the rate of metabolism and renal excretion have been observed. Slow metabolizers and excreters are more prone to suffer from drug toxicity following routine therapeutic doses.

Adverse reactions:

(i) **Local irritation:** Oral streptomycin may occasionally cause nausea and vomiting. Sterile injection abscesses and fever may develop on intramuscular administration and injection into a nerve may result in pain and paresis. Intrathecal injection can result in a shock like state with pyrexia, respiratory depression, nystagmus and convulsions.

(ii) **Intolerance:** The manifestations include various skin rashes accompanied by eosinophilia, drug fever and lymphadenopathy. Contact dermatitis may develop in persons handling it or receiving it topically. Serious manifestations like angioedema, pericarditis, exfoliative dermatitis, acute anaphylactic shock and blood dyscrasias including agranulocytosis, thrombocytopenic purpura and aplastic anemia may occasionally develop.

(iii) **Central nervous system:** The most important and serious adverse effect associated with the use of streptomycin is the damage to the 8th nerve. Streptomycin is more prone to impair the vestibular function; this is not so calamitous as deafness caused by dihydrostreptomycin, since the vestibular damage is usually reversible and the equilibrium is partly restored by ocular and deep proprioceptive sensations. The incidence of this complication is dependent on the dose and duration of streptomycin therapy; thus, nearly 75 per cent of patients given 2 g. of streptomycin daily for 2 to 4 months develop vestibular damage, while only 25 per cent are affected when a daily dose of 1 g. is employed. There is also considerable individual variation in susceptibility to the drug. The likelihood of ototoxicity is greater in premature babies, infants, elderly patients who are dehydrated and those with impaired renal function. Intrathecal administration is more likely to cause vestibular damage than intramuscular administration.

The labyrinthine dysfunction presents itself with a moderately severe headache which precedes the acute illness in which nausea, vomiting, giddiness, ataxia and nystagmus develop. These persist for 8 to 15 days. The acute stage is usually followed by chronic labyrinthitis which persists for 40 to 60 days and in which ataxia is the most prominent feature. With stoppage of the drug, full recovery occurs within 12 to 18 months, but in some cases residual dysfunction may persist. The patient, therefore, should be forewarned of the possibility of vestibular impairment before prolonged streptomycin therapy is initiated.

Streptomycin may also cause deafness though this is not so common. It is usually preceded by tinnitus. A few cases of congenital loss of hearing have been reported following the administration of this drug to mothers during the 2nd trimester of pregnancy.

Other rare toxic effects on the nervous system include optic neuritis and peripheral neuritis. As chloramphenicol is also capable of producing optic neuritis, the two drugs should not be combined for systemic administration. Circumoral paraesthesia may occur within 30 to 60 minutes after intramuscular streptomycin and persist for several hours.

(iv) **Skeletal muscle:** Streptomycin like neomycin, kanamycin, polymyxin B and colistin, has a potential curarimimetic action, producing neuromuscular block and respiratory arrest on intrapleural or intraperitoneal instillation. This effect is unusual on intramuscular use. It acts by inhibition of Ach release from the pre-ganglionic terminals through competition with calcium ions. The blockade can be antagonized by calcium salts and by neostigmine.

(v) **Kidney:** Mild albuminuria and cylindruria may occur in patients receiving streptomycin, but azotemia is rare. In patients with inadequate renal function, streptomycin can accelerate the development of azotemia. Renal irritation, however, occurs only with doses of 3 to 4 g. per day.

(vi) **Superinfection:** Superinfection with *Staph. aureus* and *Candida* on either local or systemic administration of streptomycin has been reported. Endocarditis due to candida and staphylococcal enterocolitis can occasionally be fatal.

Preparations and dosage:

(i) Streptomycin sulfate I.P. is a white hygroscopic powder with a slightly bitter taste, freely soluble in water. It is the most commonly employed salt of streptomycin.

(ii) Streptomycin injection I.P.: Dose: 0.5 to 1 g. of the base daily by intramuscular injection. The intrathecal dose varies from 10 mg. in infants to 100 mg. in adults, dissolved in 10 ml. of normal saline, administered over a period of 10 minutes. The minimum interval between two intrathecal doses must be 12 hours.

(iii) Streptomycin sulfate tablet I.P. contains 0.5 g. of streptomycin base. Dose: 0.5 to 2 g. of the base daily, in divided doses. Streptomycin is also available in a syrup form for oral use.

Topical use of streptomycin is not encouraged for fear of sensitisation.

Bioassay: Streptomycin is bioassayed by its ability to inhibit the growth of *Bacillus subtilis.*

Therapeutic uses: In a country like India, with a high incidence of tuberculosis, the use of streptomycin should primarily be restricted to the treatment of this condition, as the indiscriminate use of streptomycin may result in the development of resistant tubercle bacilli in individuals with a latent tuberculous infection. The major therapeutic uses of this antibiotic are:

(i) **Tuberculosis:** See Chapter 47.

(ii) **Urinary tract infections:** Streptomycin is useful in urinary tract infections caused by *E. coli, Proteus, A. aerogenes, K. pneumoniae* and *enterococci.* (See Chapter 46).

(iii) **Meningitis:** Streptomycin in combination with sulfonamides, is commonly employed in the treatment of meningitis due to *H. influenzae*. However, development of resistance, and poor penetration of the blood brain barrier are the two major handicaps of this therapy. The drug is administered systemically in the dose of 1 to 2 g. in adults and 30 mg./kg. daily in children along with initial sulfadiazine or sulfafurazole intravenously. Streptomycin is also given intrathecally in addition, in the dose of 10 to 100 mg. Alternative drugs employed include chloramphenicol alone or in combination with sulfonamides and ampicillin. Streptomycin is also useful against meningitis due to *E. Coli, K. pneumoniae, Proteus* and *Aerobacter*.

(iv) **Bacteremia and bacterial endocarditis:** Bacteremia and endocarditis due to *Strep. fecalis* are usually treated with penicillin-streptomycin combination. Details of the treatment have been discussed earlier.

(v) **Respiratory tract infections:** Streptomycin, 1 g. every 12 hours, intramuscularly, along with oral chloramphenicol or tetracycline, has been used in the treatment of pneumonia due to *K. pneumoniae*. As the temperature falls to normal, the dose of streptomycin should be reduced to 1 g. per day and the combined therapy should be continued for a minimum period of 2 weeks. A similar combination is also useful in countering tracheobronchitis and pneumonia due to *H. influenzae*. In all these conditions tetracycline is preferred to chloramphenicol because of the possible toxicity of the combination.

(vi) **Plague:** Streptomycin is highly specific in the treatment of plague. The specific therapy must be instituted within first 15 hours of overt illness, particularly in plague pneumonia, to ensure a favourable response. Streptomycin is administered in the dose of 4 g. daily for 2 days followed by 2 g. daily given for further 5 days. However, because of its toxicity, tetracyclines are usually preferred. Supportive care includes the use of intravenous fluids and vasopressor drugs to combat hypotension and shock and oxygen therapy, particularly in the presence of pneumonitis. Tracheostomy is often useful for improving pulmonary function.

(vii) **Tularemia:** This infection is highly sensitive to streptomycin and most cases respond to a parenteral dose of 1 to 2 g. daily for 7 to 10 days.

(viii) **Brucellosis:** Streptomycin 2 g. daily, along with 2 g. of a tetracycline daily, for a period of 2 to 3 weeks, is the treatment of choice in this condition.

(ix) **Miscellaneous:** In the treatment of peritonitis, streptomycin 2 to 4 g. daily in divided doses is administered along with 2 to 4 million units of benzylpenicillin daily for 8 to 10 days. Streptomycin may be used in the treatment of chancroid and granuloma inguinale in the dose of 2 g. daily, in patients allergic or resistant to standard chemotherapy. In granuloma inguinale, treatment should be continued for 5 to 10 days. Streptomycin can be used orally, in the dose of 2 to 3 g. daily for intestinal asepsis and in the treatment of acute bacillary dysentery. The drug may be injected intrapleurally in the dose of 0.5 to 1 g. for the treatment of empyema.

KANAMYCIN (Kancin): This water soluble aminoglycoside antibiotic is derived from *Streptomyces kanamyceticus*.

Antibacterial action: Kanamycin is effective against many Gram-negative organisms including *E. Coli, Klebsiella Aerobacter, Salmonella, Shigella, Vibrio M. tuberculosis, atypical mycobacteria, Neisseria* and *Brucella*. Certain indole positive strains of proteus are sensitive to this antibiotic. The *staphylococci* are also inhibited by low concentrations of kanamycin. The antibiotic is bactericidal. Although resistance to kanamycin can occur, unlike in the case of streptomycin, it is a slow process. Such organisms may show complete cross-resistance to neomycin and paromomycin as well as one way cross resistance to streptomycin i.e. organisms resistant to kanamycin may be resistant to streptomycin, but organisms resistant to streptomycin may be sensitive to kanamycin.

Absorption, fate and excretion: Almost the entire quantity of the drug administered orally is excreted unchanged in feces. On intramuscular administration kanamycin behaves like streptomycin in regard to blood levels, distribution and excretion. It is not significantly bound to plasma proteins. Like streptomycin, it is excreted mostly by glomerular filtration. In the presence of renal damage, the antibiotic accumulates in the body. Significant amounts are excreted in the bile. The drug does not cross the placental barrier in significant quantities.

Adverse reactions: Toxicity of kanamycin is similar to that of streptomycin. The major toxic effects are 8th nerve damage, nephrotoxicity and a curariform action on skeletal muscles. Damage to the cochlear division occurs more frequently. The damage is not completely dose dependent as marked impairment of hearing and even permanent deafness have been recorded after the use of generally accepted doses. In addition to allergic manifestations it causes irritation at the site of injection. Prolonged oral therapy may cause superinfection by fungi and yeasts, deficiency of vitamin K due to destruction of intestinal flora, diarrhoea and intestinal malabsorption. This must be remembered particularly in patients with decompensated hepatic cirrhosis. Usually, the changes induced by this drug revert to normal after discontinuation of therapy.

Renal damage with kanamycin is a toxic tubular effect characterised by pyuria, hematuria, proteinuria and cylindruria. Acute tubular necrosis may develop occasionally. Hence, if kanamycin sulfate is to be used in an anuric patient, it should be given in the initial dose of 1 g. followed by 0.5 g. repeated at the interval of 2 to 4 days; during recovery, the dose is repeated at the interval of 1 to 2 days.

Respiratory and cardiac arrest following 1 g. of intravenous kanamycin has been described. This effect is secondary to its curariform action, similar to that of streptomycin.

Preparations and dosage: The adult intramuscular dose of kanamycin for systemic infections is 1 to 1.5 g. daily in 2 or 3 divided doses. The upper limit of total 1.5 g. should not be exceeded; for children, the intramuscular dose is 10-15 mg. per kg. daily. Because of the potential toxic effects of the antibiotic, treatment should not be continued for more than 10 days. In severe peritonitis, the intramuscular therapy is supplemented by intraperitoneal injection of 250 mg. of kanamycin in 500 ml. of normal saline twice daily. The intrathecal dose of kanamycin is 25 to 50 mg. daily diluted to 10 ml. with normal saline. It has been administered as an aerosol under intermittent positive pressure and also as an irrigating solution (0.25 per cent) in abscesses and body cavities.

For intestinal asepsis, the drug is administered orally in the dose of 4 g. daily. Extensive ulcerative disease of the bowel may allow enhanced absorption of kanamycin after oral administration.

Therapeutic uses: Although it is effective against certain Gram-positive organisms, the parenteral use of kanamycin is restricted to the treatment of certain fulminating systemic Gram-negative infections because of its potential toxicity. Such therapy, whenever possible, should be guided by the results of bacterial sensitivity tests. Orally, the drug is used for sterilizing the gastrointestinal tract. The major indications for its use are—

(i) Fulminating urinary tract infections with septicemia due to *E. coli, Proteus, A. aerogenes* and *K. pneumoniae*. Such an infection may complicate pyelonephritis of pregnancy or puerperium. Its therapeutic efficacy is enhanced by alkalinization of urine. The use of this antibiotic in the treatment of urinary tract infections is discussed in Chapter 46.

(ii) *Septicemia, meningitis and bacterial endocarditis due to Gram-negative organisms:* Septicemia due to Gram-negative organisms with or without peritonitis is treated with intramuscular kanamycin. In the event of peritonitis the drug is instilled into the peritoneal cavity in addition to intramuscular injections. Bacterial endocarditis due to Gram-negative organisms is treated with 0.25 to 0.5 g. of kanamycin intramuscularly, 4 times daily. Kanamycin is a useful drug in the treatment of *E. coli meningitis* in neonates, where it is given by intrathecal as well as by intramuscular route.

(iii) Kanamycin is also used occasionally as a secondary drug in the treatment of tuberculosis but its high toxicity precludes its routine use in this condition.

(iv) Kanamycin is used orally to suppress the intestinal flora prior to surgery, in infantile gastroenteritis due to *E. coli* and as an adjunct therapy in cases of hepatic coma.

GENTAMICIN (Garamycin, Genticin): This aminoglycoside antibiotic is produced by *Micromonospora purpura* and is available as sulfate.

Antibacterial activity: Gentamicin is effective against *pseudomonas, E. coli, Proteus, A. aerogenes, K. pneumoniae, Salmonellae* and Group A beta *hemolytic streptococci*. *Staphylococci* are also highly sensitive including those resistant to penicillin, neomycin and kanamycin. The inhibitory concentration of gentamicin for these organisms is lower than that of neomycin or kanamycin. The most significant point is that gentamicin is effective against *Pseudomonas aeruginosa*. *M. tuberculosis* and *mycoplasma pneumoniae* are highly sensitive. It can produce a bactericidal effect. Resistance develops slowly and cross resistance to kanamycin and neomycin can occur.

Absorption, fate and excretion: Gentamicin is not significantly absorbed on oral administration and may be used by this route as an intestinal antiseptic. After intramuscular administration of a single therapeutic dose, peak plasma levels are reached within 60-90 minutes and the therapeutically effective concentration persists for 6-8 hours. Diffusion of the drug into the body fluids are inadequate. Approximately 25 to 30 per cent of the drug is bound to plasma proteins. It is mainly excreted by glomerular filtration and its urinary concentration ranges from 50 to 100 times that in the plasma. High plasma levels are seen in patients with impaired renal function.

Adverse reactions: Allergic skin reactions and possibly photosensitivity reactions have occurred following topical gentamicin therapy. Parenteral drug therapy, particularly in the presence of renal impairment, may produce vestibular damage and oto-toxicity. Dizziness is the main presenting symptom. A transient rise in blood urea nitrogen has also been reported in some patients. The drug should be avoided in pregnancy.

Preparations and dosage: For treatment of acute bacterial enteritis and pre-operative preparation of the bowel, 100 to 800 mg. of the drug may be administered orally daily in divided doses. A 0.1 per cent cream or ointment is used for topical application.

The intramuscular dose of the drug is 80 mg. in 2 ml. at 8 hourly intervals for patients with normal renal function. The dose should be reduced in the presence of renal damage. The drug can also be given intrathecally, in the dose of 5 mg. in adults and 1 mg. in infants per day.

Therapeutic uses:

(i) **Local infections:** Gentamicin has been employed in a wide variety of infected skin lesions. It is useful in treating cases of burns infected with pseudomonas, bed sores and the nasal carriers of staphylococci.

Gentamicin administered orally is useful in the treatment of gastrointestinal infections caused by susceptible organisms and for pre-operative preparation of the bowel.

However, it does not appear to be superior to neomycin for this purpose. It is also much more expensive.

(ii) **Systemic infections:** Although several Gram-positive bacteria are susceptible to gentamicin, safer and equally or more effective agents are available for treating infections caused by these bacteria. Gentamicin is highly effective against the important pathogens of the urinary tract, particularly the pseudomonas and a few cases of pneumonia, septicemia and meningitis due to this organism have also been successfully treated. In *Ps. aeruginosa* infections, gentamicin and carbenicillin have been shown to act synergistically.

The antibacterial activity of gentamicin is additive with ampicillin but with chloramphenicol and tetracyclines reduction in therapeutic effect may occur. Its combination with cephalosporins can cause acute renal tubular necrosis.

TOBRAMYCIN (Nebcin): This aminoglycoside antibiotic is derived from the actinomycetes *Streptomyces tenebrarius*. It has spectrum and toxicity similar to that of gentamicin. It is bactericidal and is more active than gentamicin against *Ps. aeruginosa*. It is administered intramuscularly in the dose of 3-5 mg/kg./day in 3-4 equal doses. It can also be given intravenously, well diluted and slowly. Like other aminoglycoside antibiotics, it should be used cautiously and in smaller doses in patients with impaired renal function.

AMIKACIN is a semisynthetic aminoglycoside with pharmacokinetic properties similar to those of kanamycin. Its therapeutic uses and adverse reactions are similar to those of gentamicin. The drug is active against gentamicin resistant organisms such as *Ps. aeruginosa*, *Klebsiella*, *E. coli* and *Proteus*.

From among gentamicin, amikacin and tobramycin, gentamicin is the most active against all gentamicin sensitive bacilli except *Ps. aeruginosa* which is probably more sensitive to tobramycin.

Sisomycin and **Verdamycin** are other aminoglycosides with gentamicin like properties, which are under evaluation.

PAROMOMYCIN (Humatin): This antibiotic obtained from a strain of *Streptomyces rimosus* has a similar spectrum of activity and toxicity as neomycin. It also shows considerable activity against *E. histolytica*. The drug is not absorbed on oral administration. Adverse effects of oral therapy include headache, emesis, diarrhoea and skin rashes; superinfection with Candida may occur after prolonged oral therapy. Paromomycin is usually administered initially in a loading dose of 4 g. followed by 2 g. daily in four divided doses. Smaller doses are used in children. The drug has been used in chronic bacillary dysentery, for sterilization of the bowel before surgery and in hepatic coma. Its use in the treatment of amoebiasis is discussed in Chapter 51.

NEOMYCIN: This antibiotic, obtained from *Streptomyces fradiae*, is a polybasic, water soluble substance relatively stable to heat and changes in pH. It is commonly used as a sulfate complex which is extremely stable at room temperature in dry state or in the form of an aqueous solution.

Antibacterial activity: Neomycin is effective against a wide variety of Gram-positive and Gram-negative organisms including *Enterococci, Streptococci, Staphylococci, B. anthracis, C. diphtheriae, H. Influenzae, H. pertussis, Proteus, Pasteurella, Vibrio comma, Salmonella* and *Shigella*. The antibiotic is bactericidal. Resistance to the antibiotic is noted and the organisms show cross resistance to kanamycin.

Neomycin is poorly absorbed on oral administration and hence, is used as an intestinal antiseptic. In the presence of hepatic or renal disease or in patients with extensive ulcerative bowel lesions, the drug may produce systemic toxicity. Systemic use of neomycin is not recommended because of its high toxicity.

Neomycin is administered orally in the dose of 4 to 8 g. per day. Dermatological and ophthalmic ointments containing 5 mg. of the drug per g. are available. These are applied twice or thrice daily.

Adverse reactions: The toxicity of parenteral therapy is similar to that of streptomycin. It is highly toxic to the 8th nerve.

Serious ototoxicity, nephrotoxicity and respiratory paralysis can also occur following its topical application to burns or ulcers and local intestinal use.

Neomycin, administered orally in maximal daily doses, may cause malabsorption. Gastrointestinal and systemic superinfection with resistant staphylococci and candida may complicate prolonged oral therapy.

Therapeutic uses:

(i) For topical application to the skin and eye; it is usually combined for this purpose with other antibiotics like bacitracin or polymyxin to prevent the emergence of resistant strains and to widen the spectrum;

(ii) As an intestinal antiseptic prior to colonic surgery and for suppression of intestinal flora in hepatic failure;

(iii) In the treatment of gastroenteritis due to pathogenic *E. coli* and paracolon bacilli;

(iv) For irrigation of the bladder; the strength commonly used is 40 mg. of neomycin with 20 mg. of polymyxin per litre of solution.

FRAMYCETIN (Soframycin): This antibiotic, produced by *Streptomyces decaris* is used as the water soluble sulfate salt. The antimicrobial spectrum and toxicity of framycetin are similar to those of neomycin. According to some authorities, this antibiotic is identical with Neomycin B though this is denied by manufacturers. The use of this antibiotic is restricted only to topical application and oral administration for local action on the gastrointestinal tract. The antibiotic is not absorbed from these sites.

Framycetin sulfate, as a 0.5 per cent ointment, cream or solution is used for staphylococcal skin infections and in the treatment of nasal carriers of staphylococci.

COLISTIN: This polypeptide antibiotic, chemically identical with polymyxin E is obtained from the bacterium, *Aerobacillus colistinus.*

Antibacterial activity: Colistin is bactericidal to many Gram-negative organisms e.g. *H. pertussis, Pseudomonas, E. coli, A. aerogenes, K. pneumoniae, H. influenzae* and *Shigella.* Most strains of Proteus and the Gram-positive organisms are resistant to it. Resistance to the antibiotic appears slowly. There is a complete cross-susceptibility as well as cross resistance between colistin and polymyxin.

Absorption, fate and excretion: Colistin, administered orally, is not significantly absorbed and hence, may be administered by mouth in the treatment of certain Gram-negative infections of the gastrointestinal tract. However, a significant amount of the drug is absorbed on oral administration in infants.

After intramuscular administration of a therapeutic dose, peak plasma levels are reached within 1 hour and decline by 6 hours. The preparation employed for intramuscular administration, sodium colistimethate undergoes hydrolysis to release the active antibiotic in the tissues, this leads to fluctuations in the plasma levels. Colistin does not enter the CSF in adequate concentrations even in the presence of meningeal inflammation. The drug is mainly excreted in urine. The urinary concentration of the active drug is 5 to 20 times higher than its plasma level.

Adverse reactions: These occur in as many as 30 to 50 per cent of patients and include pain at the site of injection, circumoral and lingual paraesthesiae, nausea, skin rash, pruritus, vertigo, ataxia, nystagmus and azotemia especially in patients with previously impaired renal function. Acute renal failure can also occur; rarely fatal proximal tubular necrosis may develop. Because of the potential nephrotoxicity of this drug, frequent determination of the serum creatinine during its use is mandatory. Other serious toxic effects include partial deafness, leukopenia, granulocytopenia, hepatotoxicity and transient disturbances of vision and speech. The drug has a curariform effect. Superinfection with proteus may occur during oral as well as systemic treatment with colistin.

Preparations and dosage:

(i) Colistin sulfate is marketed as a dry powder for oral administration and as a paediatric suspension. Dose: 3 to 5 mg. per kg. daily, given in 3 equal portions.

(ii) Sodium colistimethate. This is a sulfomethyl derivative of colistine. It is relatively painless on intramuscular injection, less toxic but less active antibacterially. Dose: 2.5 to 5 mg. per kg. daily given in 2 or 3 divided doses. Intrathecal and intravenous routes are not recommended.

Therapeutic uses: Colistin is usually reserved for fulminating infections, caused by *Pseudomonas*, resistant to other chemotherapeutic agents. The drug is particularly valuable in the treatment of urinary tract infections due to Pseudomonas. It can be used in other Gram-negative infections resistant to the more commonly used chemotherapeutic agents. It may be used orally in the treatment of pseudomembranous enterocolitis caused by pseudomonas and in shigella enteritis.

POLYMYXIN B (Aerosporin): Polymyxin is the generic name for a group of closely related polypeptide antibiotics elaborated by various strains of *Bacillus polymyxa*. Polymyxin B, initially thought to be the least toxic of these antibiotics, is used in therapy as a sulfate. Polymyxin E was discarded but is now once again used after its rediscovery as colistin.

The antibacterial activity, absorption and metabolism of polymyxin are similar to that of colistin and like colistin, it is bactericidal. However, *in vitro*, weight for weight, it is more potent than colistin. It is mainly excreted by the kidneys.

Adverse reactions: The drug shares all the toxic manifestations of colistin. It is more toxic than colistin.

Preparations and dosage: Polymyxin B sulfate intramuscular injection; dose 1.5 to 2.5 mg. per kg. daily in 3 equally divided doses. Polymyxin B may also be administered intrathecally; the dose in children is 2 mg. daily for 3 to 4 days followed by 2.5 mg. on alternate days, while for adults, 5 mg. are given daily for first 3 to 4 days followed by 5 mg. on alternate days. For topical administration, 0.1 to 0.25 per cent sterile isotonic solutions are employed. The amount of the drug applied to open wounds should not exceed 200 mg. A sulfomethyl derivative of polymyxin (Thiosporin) is available for intramuscular use.

Therapeutic uses: Indications are similar to those for colistin. However, it has been found that in order to achieve activity against *pseudomonas* equal to that of polymyxin B, colistin may have to be used in doses higher than those generally recommended, which carries a greater risk of clinical toxicity when compared with the smaller doses of the more potent polymyxin B. Unlike colistin, polymyxin B can be administered intrathecally or intravenously. Polymyxin B, therefore, is now preferred to colistin in the treatment of fulminating and resistant infections caused by pseudomonas.

Polymyxin B may be inhaled in the form of an aerosol several times a day in the treatment of susceptible pulmonary infections. The drug has also been used topically for the treatment of superficial infections caused by Gram-negative organisms.

TYROTHRICIN: This antibiotic, obtained from *Bacillus brevis*, is in fact, a 80:20 mixture of two antibiotics, Tyrocidine and Gramicidine, respectively. Tyrothricin is bacteriostatic. Gramicidine is more potent than Tyrocidine and is particularly effective against *Pneumococci*, *Streptococci*, *Staphylococci* and *C. diphtheriae*. Tyrocidine has a weak antibacterial action against these and in addition, exhibits a mild antibacterial action against certain Gram-negative organisms.

Tyrothricin is ineffective orally and is too toxic parenterally. It is employed only for topical therapy in the form of alcoholic solution and ointment to treat infected superficial ulcers, wounds, pyodermas and indolent corneal ulcers and as troches in otorhinolaryngeal infections.

CYCLOSERINE: This antibiotic, obtained from *Streptomyces orchidaceus* is mainly used as a second line drug in the treatment of tuberculosis but may also be employed in the treatment of resistant *E. coli* infections of the urinary tract. The details are discussed in Chapters 46, 47.

SPECTINOMYCIN: This antibiotic derived from *Streptomyces spectabillis* has a moderate *in vitro* activity against many Gram-positive and Gram-negative bacteria. Although it is not an aminoglycoside, like streptomycin it contains a cyclic amino polyol (aminocyclitol) group. Resistance tends to develop rapidly by certain microorganisms, particularly the staphylococci. It is now mainly used to treat gonorrhoea, as an alternative to penicillin. It is not effective in syphilis. It is usually administered in the dose of 2-4 g. intramuscularly. Adverse effects reported include nausea, insomnia, and allergic reaction.

43

Antibiotics Effective Against Both Gram-positive and Gram-negative Organisms

Antibiotics which are effective in both Gram-positive and Gram-negative infections are: semisynthetic penicillins e.g. ampicillin, hetacillin and carbenicillin; rifamycins (see Chapter 41, 44); cephalosporins, tetracyclines and chloramphenicol. The last two are also effective against certain protozoa and 'virus like' organisms. They are discussed in Chapter 44.

CEPHALOSPORINS

A number of antibiotics have been obtained from the mould *Cephalosporium acremonium* originally recovered from Sardinian sewage. These have been termed cephalosporins. The most important antibiotic elaborated by the cephalosporium mould is cephalosporin C, a derivative of 7-amino cephalosporanic acid and many semisynthetic cephalosporins have now been prepared. So far, four cephalosporins namely cephaloridine, cephalothin, cephalexin and cephaloglycine have been extensively studied. Of these, cephaloridine and cephalothin are given parenterally since they are poorly absorbed from the gut while cephalexin and cephaloglycine are effective orally.

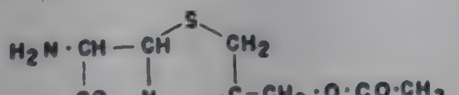

Fig. 43.1: 7-Amino cephalosporanic acid.

Antibacterial activity: Cephalosporins possess a wide range of activity against Gram-positive and Gram-negative bacteria. In general, cephaloridine is the most active compound. They are effective against both penicillin sensitive and penicillin resistant Staphylococci, Pneumococci, *C. diphtheriae* and Group A and beta hemolytic streptococci. None, however, is as active as benzylpenicillin against penicillin sensitive staphylococci and certain staphylococcal strains show relative resistance to the bactericidal activity of these antibiotics probably because the drug is to some extent destroyed by penicillinase.

The Gram-negative organisms susceptible to these antibiotics include *E. coli, Proteus mirabilis, K. pneumoniae, N. gonorrhoea* and *Paracolobacterium* species. Cephaloridine shows good activity against *S. typhi* and *paratyphi*, and is also effective against some strains of Shigella. The antibiotics are ineffective against *Pseudomonas aeruginosa*, Enterobacter, indol positive proteus and Bacteroides. They have a limited activity against *H. influenzae* and *Str. faecalis.*

Resistance to cephalosporins develops slowly *in vitro* and is independent of penicillin resistance in the case of staphylococci.

Cephalosporins act by inhibition of bacterial cell wall synthesis and are bactericidal.

CEPHALORIDINE AND CEPHALOTHIN: Cephaloridine (Ceporan) being water soluble is used as the base while cephalothin is used as a sodium salt. These are administered by intramuscular or intravenous injection.

After intramuscular administration of a therapeutic dose of cephalothin, peak plasma levels are obtained within 15 to 30 minutes and a negligible concentration remains in the plasma after 4 hours. In contrast, peak plasma concentration with cephaloridine is achieved within 40 to 60 minutes and is roughly 50% higher than that reached with an equivalent dose of cephalothin. Significant antibacterial activity can be detected in plasma upto 8 hours.

All cephalosporins do not bind to serum proteins to the same extent. Approximately 50 per cent of cephalothin is bound to plasma proteins and nearly 33 per cent of the administered dose is metabolized by the liver whereas the remainder is excreted mainly by renal tubular secretion. It is excreted rather more rapidly than cephaloridine: over 95% of an administered dose of cephalothin can be recovered from the urine within six hours. Cephalosporins are relatively slowly excreted by infants and premature children. The penetration of cephalosporins into the CSF is poor and they should not be used to treat bacterial meningitis.

Protein binding is insignificant with cephaloridine. Further, it is insignificantly metabolized in the liver, the major portion is excreted mainly by glomerular filtration and only a minimal amount by tubular secretion. About 75% of a single dose of cephaloridine can be recovered from the urine in about eight hours. Since cephaloridine is mainly excreted by the kidney, the dosage schedule for this compound will require greater modification in renal failure than that for cephalothin.

About 60-80% of a dose of cephalothin is eliminated in unchanged form in the urine by renal tubular secretion. The tubular secretion of cephalothin can be blocked by probenecid but its effect on cephaloridine serum level is negligible unless very large doses are given. The concentration in the CSF is not significant.

Adverse reactions: The sodium salt of cephalothin may produce pain at the site of intramuscular injection and thrombophlebitis when given intravenously. This effect is less likely to occur with cephaloridine. The adverse effects of cephalothin include skin rash, fever, serum sickness, anaphylactoid reaction, eosinophilia, neutropenia, transient splenomegaly, increased SGOT levels and increased azotemia. A false positive Coomb's test may occur in as many as 60 per cent of patients on cephalothin therapy. Superinfection with Pseudomonas, Klebsiella-Aerobacter and bacteroides may occur during therapy. Administration of large doses of the sodium cephalothin may aggravate cardiac or renal edema.

Cephaloridine shares the adverse effects of cephalothin. Prolongation of prothrombin time is reported with this agent. Signs of cerebral irritation, nystagmus and hallucinations may occur following intrathecal administration of the drug. Large doses may cause kidney damage.

Nephrotoxicity of cephaloridine is probably dose related and is potentially reversible on drug withdrawal. It is enhanced by furosemide and other diuretics.

These antibiotics may rarely show a cross-allergy with penicillin.

Preparations and dosage: Cephaloridine is preferred for parenteral administration for obvious reasons. The adult intramuscular dose of both of these agents is 0.5 to 1 g. administered at 6 hourly intervals. For infants and children, a dose of 10 to 80 mg. per kg. should be given intramuscularly. The intravenous dose of cephaloridine is 250 mg. given through a drip, its intrathecal dose is 25 mg. in 10 ml. of normal saline daily.

CEFAZOLIN: This compound has properties similar to cephalothin. It is eliminated from body primarily by renal glomerular filtration.

CEPHALOGLYCIN AND CEPHALEXIN: These new semisynthetic cephalosporins are absorbed adequately on oral administration. Cephalexin in particular is well absorbed. Peak plasma levels with both are reached within 2 hours and decline by 6 to 8 hours. Both the compounds are secreted in urine and their renal excretion can be reduced by probenecid. However, clinical studies indicate that cephaloglycin is often ineffective in the presence of obstructive uropathy and in chronic bronchitis. Cephalexin, in contrast, administered in the dose of 500 mg. to 1 gm. every 6-8 hours, is more effective and, therefore, is more promising than cephaloglycin.

Toxicity of these two compounds is similar to that of cephaloridine. Incidence of nephrotoxicity, however, is probably less. Like other oral antibiotics, these drugs can cause gastrointestinal disturbances.

Therapeutic uses: These drugs are quite expensive at present and their use should be restricted only to special circumstances such as:

(i) Gram-positive infections resistant to penicillin or in patients allergic to penicillin. These include pneumococcal, streptococcal and staphylococcal infections. These antibiotics, however, are not effective in osteomyelitis because of their poor penetration into bones.

(ii) Urinary tract infections caused by *E. coli*, *Klebsiella* and *Aerobacter* or fulminating septicemia including meningitis and endocarditis due to these organisms. Here again, appropriate bacterial sensitivity tests should be carried out and therapy with these antibiotics is instituted, if other standard chemotherapeutic agents are not suitable.

CEPHRADINE is chemically closely related to cephalexin and has similar properties.

RIFAMYCINS

These are a group of antibiotics obtained from a strain of *Streptomyces mediterranei*. They are effective against a variety of Gram-positive bacteria including penicillin resistant staphylococci. Higher concentrations are also effective against *E. coli*. Rifampicin is effective against *M. tuberculosis*, the antitubercular activity claimed being equivalent to that of INH.

Rifamycin B (Rifamide) is not absorbed on oral administration. When given intramuscularly, it is mainly excreted in the bile and has been used in the treatment of cholecystitis.

The usual therapeutic dose of the antibiotic is 250 mg. twice or thrice daily by intramuscular injection. The drug may also be used by inhalation and topical application.

An important semisynthetic derivative of rifamycin SV is rifampicin. It is discussed in Chapter 47.

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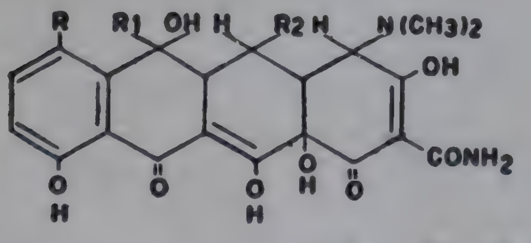
Tetracyclines, Chloramphenicol and Antifungal Antibiotics

Tetracycline antibiotics were discovered as a result of a systematic plan by the American Pharmaceutical Industry for screening a multitude of soil micro-organisms for potential antibiotic activity. The first member chlortetracycline, isolated from *Streptomyces aureofaciens*, was introduced in 1948. This was followed by oxytetracycline derived from *Streptomyces rimosus* in 1950 and tetracycline prepared by catalytic hydrogenation of chlortetracycline in 1953. Recently, other series of semi-synthetic tetracyclines have been introduced in the therapy.

TETRACYCLINES

Chemically, the tetracyclines are naphthacene derivatives. The naphthacene nucleus is made up by fusion of four partially unsaturated cyclohexane radicals and hence the name tetracyclines (Fig. 44.1). The various tetracyclines differ very slightly in structure. The crystalline bases of these compounds are pale yellow, slightly bitter and sparingly soluble in water. However, they form water soluble sodium salts. The acid salts are more stable in the dry powdered state and are usually preferred in therapy. Tetracyclines are more stable at acid pH.



	R	R_1=	R_2=
TETRACYCLINE	H	CH_3	H
CHLORTETRACYCLINE	Cl	CH_3	H
OXYTETRACYCLINE	H	CH_3	OH
DEMETHYLCHLORTETRACYCLINE	Cl	H	H

* There is no OH attached to the carbon atom to which R is attached.

Fig. 44.1: Basic structure of tetracyclines

Antibacterial activity: Tetracyclines and their semi-synthetic derivatives have similar antibacterial activity. These drugs are essentially bacteriostatic and along with chloramphenicol are termed "broad spectrum antibiotics" as, in addition to their antibacterial activity against a number of Gram-positive and Gram-negative organisms, they also inhibit the growth of certain actinomyces (fungi), rickettsiae and chlamydia organisms. Gram-positive organisms in general respond better than Gram-negative organisms.

The Gram-positive and Gram-negative organisms inhibited by tetracyclines include *Pneumococci*, *Gonococci*, some strains of *alpha* and *beta hemolytic Streptococci*, *Clostridium*, *H. influenzae*, *H. pertussis*, *H. ducreyi*, *Brucella*, *K. Pneumoniae*, *Vibrio comma* and *Donovania granulomatis*. The moderately sensitive organisms include *E. Coli*, *Aerobacter*, *Salmonella*, *Shigella*, *B. anthracis*, *P. tularensis*, *P. pestis*, *fusobacterium*, *Listeria monocytogenes* and *M. tuberculosis*. *Pseudomonas* is relatively resistant. Other organisms which respond satisfactorily are *Borrelia recurrentes*, *Mycoplasma pneumoniae* (*PPLO*), *Leptospira icterohaemorrhagiae* and *T. pallidum*. In general, chlortetracycline is relatively more active against Gram-positive cocci, oxytetracycline against pseudomonas and tetracycline against proteus. Actinomyces and Nocardia also respond but less than to penicillin. Amongst the protozoa, *E. histolytica* is inhibited only by relatively high concentrations. Tetracyclines are highly effective against rickettsial organisms and also inhibit the growth of chlamydia organisms causing lymphogranuloma venereum, psittacosis, inclusion conjunctivitis and trachoma. They are, however, ineffective against the true viruses such as those of chickenpox, small-pox, mumps and measles.

Tetracycline resistance has been demonstrated by many organisms including *Staphylococci*, *Group A streptococci*, *Pneumococci*, and *E. coli.* Resistance develops slowly *in vitro* and cross-resistance within the group is usually complete. Gram-negative organisms resistant to tetracyclines are usually resistant to chloramphenicol as well, but the tetracycline resistant Gram-positive organisms are usually susceptible to chloramphenicol.

Mechanism of action: They are postulated to act by inhibiting certain essential enzyme systems of the bacterial cell or by suppression of the bacterial protein synthesis. They appear to interfere with phosphorylation of glucose in both bacterial and mammalian cells. Tetracyclines chelate certain cations like calcium and magnesium. As these, particularly the latter, are essential for the functional integrity of various enzyme systems and ribosomes, chelation may be the basic mechanism of action of these antibiotics. Their action is partly reversed by some amino acids and vitamins, particularly riboflavin. Bacteria develop resistance slowly to these antibiotics. However, certain strains of staphylococci, streptococci, *Cl. welchii* and even pneumococci have developed resistance to tetracyclines.

Absorption, fate and excretion: The absorption of tetracyclines on oral administration is variable but adequate. Absorption increases from 25% of ingested chlortetracycline to 58% oxytetracycline and 80% of tetracycline. Doxycycline is absorbed upto over 90%. They are not destroyed by the gastric acid or the intestinal flora. The tetracyclines form insoluble complexes by chelation with calcium, magnesium and aluminium and hence, substances like milk that contain calcium and antacids reduce their absorption. Administration of iron also interferes with the absorption of tetracyclines. Experimentally, citric acid, glucosamine and phosphate have been shown to enhance the absorption of tetracycline. However, clinical comparison of capsules of these different products with capsules containing tetracycline with lactose revealed no remarkable difference when given in the same doses. Food as such does not interfere with the absorption of tetracyclines.

The tetracyclines are mainly absorbed from the stomach and upper small intestine. With increased doses, proportionately more of the drug escapes absorption and may produce gastro-intestinal disturbances.

After oral administration of a single therapeutic dose of tetracycline peak plasma level is reached within 2 to 4 hours. These drugs have plasma half-lives in the range of 6 to 9 hours. Hence, oxytetracycline and tetracyclines are usually administered at 6 hourly intervals in order to maintain their therapeutic concentrations in plasma. Oxytetracycline and tetracycline given intramuscularly, produce peak plasma levels within 1 hour and adequate levels are maintained for 12 hours; the injection, however, is painful.

The tetracyclines are widely distributed in the body and their diffusion into various body fluids, including the CSF, and glandular secretions is very much like that of penicillin. Significant quantities are detected in bile and a closed enterohepatic circulation has been demonstrated, particularly for chlortetracycline. The compounds are concentrated in liver, spleen, bone marrow, enamel of unerupted teeth and lung. They appear in saliva and semen but their concentration in the ocular fluids is poor. They cross the placental barrier and are also secreted in milk.

The tetracyclines are excreted mainly in urine by glomerular filtration. Urinary excretion is maximum with tetracycline and nearly 20 to 55 per cent of a single oral dose of the drug is excreted in the active form in urine within 24 hours. With oxytetracycline the comparable figure is 10 to 35 per cent while chlortetracycline is mainly dependent on biliary excretion and only 5 to 10 per cent of the orally administered compound can be detected in urine in the active form within 24 hours. In anuria, the plasma half-life of tetracycline is 4-5 days and that of oxytetracycline is 2-3 days.

Adverse reactions: Tetracyclines, in general, have a low toxicity when used in recommended dosages. The adverse effects are:

(i) **Intolerance:** Skin rashes are uncommon with systemic therapy but may develop on topical application of these agents. Severe allergic responses like drug fever, exfoliative dermatitis and anaphylactic shock may develop occasionally. Blood dyscrasias including aplastic or hemolytic anemia, leucopenia and thrombocytopenia are very rare.

Photosensitivity manifested by marked erythema with or without sunburn and even vesicular exanthema have been reported with tetracycline therapy. A brown-black discoloration of nails accompanied by marked loosening may also occur. In some cases, simultaneous discoloration of the teeth has been observed. These lesions may disappear on discontinuation of treatment.

(ii) **Gastrointestinal tract:** Nausea, vomiting, epigastric distress and loose stool are relatively common side effects. Nausea and vomiting may be prevented by taking these drugs after meals. Larger individual doses increase the irritation.

Diarrhoea secondary to irritation is not accompanied by erythrocytes or pus cells in feces and can thus be differentiated from diarrhoea secondary to superinfection of the gastrointestinal tract. There is some evidence that gastric irritation is less with tetracycline than with oxy- or chlortetracycline.

These symptoms appear to be dose-dependent and are more commonly observed following the doses of 2 g. or more, than when the dose is limited to 1 g. daily.

(iii) **Superinfection:** Suppression of the normal intestinal flora with resultant superinfection is liable to occur after prolonged tetracycline therapy, particularly in patients with diabetes mellitus, leukemia, leucopenia or when steroid therapy is being given simultaneously.

Infection with *Candida albicans* is especially common and may result in diarrhoea or soft, bulky, odourless stools, soreness and redness of the mouth (thrush), glossitis, black hairy tongue and inflammatory lesions of the vulva, vagina and perianal region causing troublesome pruritus vulvae or pruritus ani. Rarely, the superinfection may involve the respiratory passages. A fulminating septicemia with candida may occasionally develop. Treatment with antifungal agents is only indicated in serious cases or if the lesions persist even after stoppage of tetracyclines. Nystatin or hamycin is effective locally in oropharyngeal, vaginal and perineal lesions. Serious systemic infections may need therapy with Amphotericin B. Most of the yeast infections are generally limited to the duration of therapy with tetracyclines and routine prophylaxis with antifungal antibiotics is unnecessary.

Superinfection with *Staphylococcus aureus* occurs more frequently in hospitalized patients and may result in fever, pharyngitis, dysphagia and hoarseness of voice. Serious staphylococcal enteritis is heralded by sudden loss of appetite, abdominal discomfort or pain and distension. It is characterised by a profuse watery diarrhoea and the stools show the presence of blood, large number of pus cells and Gram-positive organisms. It carries a mortality rate of 40 per cent. Immediate stoppage of tetracyclines, institution of an appropriate antibiotic therapy and correction of dehydration and electrolyte imbalance are recommended. Rarely, staphylococcal septicemia may develop.

Pseudomembranous colitis characterised by profuse diarrhoea and fever may occur due to superinfection with *Proteus* or *Pseudomonas*. The stools contain shreds of mucous membrane. Rarely, overwhelming septicemia with proteus may develop.

(iv) **Liver:** Fatal hepatic dysfunction with pancreatitis may occur in patients receiving large doses of tetracyclines over short periods, particularly by intravenous route. Such patients develop jaundice, azotemia, acidosis, hypocalcemia, hemorrhagic diathesis, hypotension and coma. Autopsy often reveals extensive fatty changes in the liver. Pregnancy, particularly when associated with pyelonephritis, hepatic damage, renal impairment and concurrent use of other hepatotoxic drugs may enhance this hepatotoxic action. It is advisable not to exceed the dose of 1 g. per day when tetracyclines are administered intravenously in pregnant women. In fact tetracyclines be better avoided, in the interest of both mother and foetus, in pregnancy.

(v) **Kidney:** In patients with significant renal impairment, tetracyclines may cause an aggravation of azotemia. Such an effect may also develop when a tetracycline is added to solution employed in peritoneal dialysis for markedly azotemic patients. It appears that the anti-anabolic effect of tetracyclines is exaggerated in the presence of renal impairment. They should, therefore, be avoided in such cases.

A reversible 'Fanconi-like' syndrome, characterised by nausea, vomiting, proteinuria, glycosuria, acidosis and gross amino aciduria may develop after ingestion of outdated tetracycline capsules. It is attributed to a degradation product, epianhydrotetracycline. The formation of this toxic product is promoted not only by warmth and moisture but also by an acid pH, with change of colour from yellow to brown. Hence, citric acid, once included in the capsule to promote absorption of tetracycline, has now been abandoned.

(vi) **Antianabolic effect:** Tetracyclines, when administered in doses exceeding 1 g. daily for prolonged periods produce an antianabolic effect resulting in increased excretion of urinary nitrogen and certain amino acids, leading to weight loss.

(vii) **Teeth and bones:** Tetracyclines, chelate calcium, forming a tetracycline-orthophosphate complex and therefore, are deposited in areas of calcification in bones and teeth. Administration of these antibiotics to a pregnant woman may lead to yellow staining of the teeth of the infant; defective formation of enamel and hypoplasia of the teeth may also occur. Pigmentation of permanent teeth and increased risk of caries may occur in children receiving long or short term therapy with tetracyclines between 2 months and 4 years of age. The larger the dose, the greater is the risk of pigmentation.

Tetracyclines administered during pregnancy are deposited in foetal bones and may reduce their linear growth. This depression appears to be reversible. However, to prevent damage to the bones and teeth in the growing foetus, tetracyclines should be avoided after the fourth month of pregnancy unless they are a must. Tetracyclines are also deposited in nails and fluorescence of the nails may be demonstrated after prolonged tetracyclines therapy.

(viii) **Benign intracranial hypertension:** Some cases, particularly the infants, treated with tetracycline may develop increased intracranial pressure. This causes bulging of the anterior fontanella in infants and headache, photophobia and papilloedema in adults.

(ix) **Miscellaneous:** Intravenously administered tetracyclines may cause local thrombosis. They may interfere with blood coagulation, especially in those having a bleeding tendency; this effect is probably secondary to calcium chelation. Tetracyclines, like the sulfonamides, may cause acute transient myopia.

Uremic patients may develop peptic ulcers. Tetracyclines have been observed to inhibit urease of gastric mucosa which breaks down urea into ammonia. Ammonia probably serves to reduce gastric acidity and hence, lowering of ammonia concentration with tetracyclines leads to hyperacidity with consequent ulceration and bleeding.

Steatorrhea and deficiency of vitamin K may occur after prolonged tetracycline therapy.

Preparations and dosage:

(1) *For oral administration*: Chlortetracycline hydrochloride I.P. (Aureomycin), oxytetracycline hydrochloride I.P. (Terramycin), Tetracycline hydrochloride I.P. (Alcyclin, Resteclin, Achromycin, Tetracyn) are available in various forms for adult and paediatric use. Tetracyclines are yellow in colour and bitter in taste. For oral use, usually they are supplied as capsules or tablets containing 250 mg., as paediatric syrup containing 125 mg/5 ml or paediatric drops containing 100 mg/ml. The adult dose varies between 1 to 2 g. per day in 3-4 divided doses; for children 20-50 mg/kg. body weight, daily, in divided doses.

(2) *For parenteral administration*: Oxytetracycline and tetracycline are available for I.M. and I.V. administration. The usual I.M. dose is 100 mg. at 6-8 hrs. intervals. Because of local irritation and irregular absorption I.M. administration of tetracycline is generally not satisfactory. Intravenous preparations may be used in severe infections and in patients having nausea and vomiting. The total daily i.v. dose of oxytetracycline and tetracycline for most acute infections in adults is 0.5 to 1 g. in two equal doses at 12 hourly intervals; it is dangerous to use quantities more than 2 g. per day, parenterally. Administration by i.v. drip is, however, perferred. For this, tetracycline (Resteclin I.V.) 250 mg. is dissolved in 10 ml. sterile water and further diluted with 5% dextrose or normal saline so as to achieve the concentration of 1 mg./ml. It may be given slowly at the rate of 5 ml. per min. The recommended daily dose for infants and children is usually 10-20 mg/kg. body weight.

The tetracyclines are never administered intrathecally.

(3) Ophthalmic ointments and eye drops containing tetracyclines are available. The usual concentration of a tetracycline in such preparations is 0.5-1%.

Bioassay: The tetracyclines are bioassayed by their inhibitory effect on the growth of *Bacillus pumilus*.

NEW TETRACYCLINES

These compounds have a better absorption, a longer duration of action or greater felicity of parenteral administration than the older tetracyclines. Their antibacterial spectrum does not differ from that of the parent compounds and they may offer only marginal advantages, some times at a higher cost. The important agents of this class are:

(a) DEMETHYLCHLORTETRACYCLINE (Ledermycin): This tetracycline differs from chlortetracycline by the absence of a methyl group. It is more stable to temperature and pH changes than the other analogues. The antibacterial activity of this drug is claimed to be more than that of tetracycline against most species of organisms.

After oral administration, demethylchlortetracycline is better absorbed than other tetracyclines and maximum blood levels are reached within 3 to 6 hours. Approximately 40 to 50 per cent of the drug is bound to plasma proteins. The concentration attained in the CSF is poor; however, it tends to diffuse into other body cavities and into relatively ischemic tissues. The drug is slowly excreted by kidneys and therapeutic blood levels are claimed to be maintained for at least 24 hours after cessation of treatment.

Demethylchlortetracycline shares all the adverse effects of the tetracyclines. The incidence of photosensitivity reactions is higher with this antibiotic. Nephrogenic diabetes insipidus has also been reported after its use.

The dosage of the drug depends upon

the severity of infection and sensitivity of the pathogenic organisms involved. The usual adult dose is 600 mg. daily in 2 or 3 divided doses. For infants and children, a dose of 6 to 12 mg. per kg. daily in 2 or 3 divided doses is given.

(b) METHACYCLINE (Rondomycin): This antibiotic shows almost identical *in vitro* activity as demethylchlortetracycline. After oral or intravenous administration, methacycline gives higher and better sustained blood levels because its protein binding is similar to that of demethylchlortetracycline. However, it is more rapidly excreted than the latter.

(c) LYMECYCLINE: This is a tetracycline made soluble by combining it with the amino acid lysine. The drug is claimed to be almost completely absorbed on oral administration and is also preferred for intramuscular use as it is less irritant. Available evidence suggests that 150 mg. of lymecycline are therapeutically equivalent to 250 mg. of the standard tetracyclines.

(d) DOXYCYCLINE (Vibramycin, Vivocycline): This antibiotic, administered orally, appears to be better absorbed and more slowly excreted than demethylchlortetracycline and methacycline. The blood levels obtained with 100 mg. of doxycycline are higher and more sustained than with 300 mg. of demethylchlortetracycline. Serum levels persist for 24 to 36 hours after cessation of therapy. With a single dose of 500 mg. serum level of 1 μg per ml has been reported to be present upto 4 days.

The plasma half life of doxycycline is not significantly affected by renal insufficiency and the drug does not seem to aggravate azotemia in this condition. Almost 90% of the drug is excreted in the faeces in inactive form.

The drug is available in 100 mg capsules. The recommended dose in adults is 100-200 mg. once a day. In severe infections, a dose of 100 mg. every 12 hours is recommended. For children, a dose of 3-4 mg. per kg. daily is given initially in 2 divided doses. For severe infection this dose may be increased. Subsequently, a maintenance dose of 1-2 mg. per kg. is administered either as a single dose or divided into 2 doses. Doxycycline can also be given intravenously.

(e) MINOCYCLINE: This tetracycline, better absorbed from the gastrointestinal tract than demethylchlortetracycline, exhibits greater antibacterial activity than older tetracyclines. It is effective against tetracycline resistant *Staph. aureus*, *Strep. pyogenes*, *enterococci*, *meningococci* and *E. coli* and exhibits a significant activity against nocardia, asteroides and *M. tuberculosis*. It is excreted in bile and feces. The drug has better tissue penetration. However, unlike other tetracyclines it causes vestibular toxicity such as vertigo, dizziness, ataxia, nausea and vomiting.

(f) ROLITETRACYCLINE (Reverin): This is a synthetic pyrrolidinylmethyl derivative of tetracycline. It is more soluble over a wider range of pH values than the parent compound. This facilitates its intravenous administration and enhances its absorption after intramuscular use. The drug disappears slowly from the blood; a low concentration is still present in the plasma 24 hours after a single intravenous therapeutic dose. It is mainly eliminated by kidneys.

The intramuscular dosage of rolitetracycline for adults is 250 to 500 mg. twice daily. For intravenous infusion 250 to 500 mg. of the drug is dissolved in 10 ml. of distilled water and administered through normal saline or 5 per cent dextrose, 12 hourly.

Therapeutic uses: Although tetracyclines are effective against a wide range of organisms, they are not to be preferred routinely against the organisms that are highly sensitive to other equally safe bactericidal antibiotics like penicillin. Tetracyclines are indicated in:

(i) **Rickettsial infections:** The tetracyclines are very effective in rickettsial infections like murine, epidemic and scrub typhus, rickettsial pox, Q fever and Rocky mountain spotted fever. Fever subsides within 24 to 72 hours and the rash disappears within 4 to 6 days. Relapses are rare if adequate doses are employed and even if a relapse occurs, it promptly responds to retreatment. The initial dose of tetracyclines is 2 to 3 g. for first 24 hours followed by 1-2 g. daily till the temperature subsides.

(ii) **Granuloma inguinale:** This infection caused by *Donovania granulomatis* responds satisfactorily to a daily dose of 2 g. of a tetracycline given for a period of 2 weeks. If relapse occurs or if the organism becomes resistant to tetracycline, streptomycin in the dose of 2 g. daily may be given intramuscularly over a 2 week period.

(iii) **Primary atypical pneumonia:** This condition, caused by *Mycoplasma pneumoniae*, responds satisfactorily to tetracyclines, given in the daily dose of 2 g. for 6 to 7 days.

(iv) **Cholera:** The use of tetracyclines in the treatment of this infection is discussed in Chapter 34.

(v) **Chlamydia infections:** Chlamydia group of organisms are responsible for causing trachoma, inclusion conjunctivitis, lymphogranuloma venereum and psittacosis. Like the viruses, these organisms are obligate intra-cellular parasites of very small size but unlike viruses and like bacteria they multiply by binary fission. Further, their cell walls resemble those of Gram-negative bacteria. The chlamydia causing trachoma and lymphogranuloma venereum are sensitive to sulfonamides and cycloserine while those which cause psittacosis or similar infections are resistant. In both these groups tetracycline can be used.

In *psittacosis* a dosage schedule of 2 g. daily for two weeks is usually recommended. Use of tetracyclines in *lymphogranuloma venereum* is discussed in Chapter 49.

Although sulfonamides are known to be effective in *trachoma*, the tetracyclines are often equally useful. A tetracycline ophthalmic ointment may be applied in the eye 3 to 4 times daily for 4 weeks along with 3 to 4 g. oral sulfadimidine, given for 3 weeks. Adequate drug therapy early in the disease can lead to a complete healing without any sequelae but when it is started late, even though the infection is often controlled, pannus and scarring persist. In endemic areas, where adequate therapy is not possible, the antibiotic ointment may be applied twice daily on every alternate day for a period of 6 months.

Inclusion conjunctivitis responds to topical application of tetracycline ointment 4 times daily for a period of 2 to 3 weeks.

(vi) **Bacillary infections:** Use of tetracyclines in acute bacillary dysentery is discussed elsewhere. These drugs are very effective in both acute and chronic brucellosis. In severely ill patient, streptomycin in the daily dose of 2 g. along with a tetracycline 0.5 g. 6 hourly, for 2 to 3 weeks, is recommended. In a chronic infection, sulfadimidine in the daily dose of 4 g. may be added to the above therapy.

Although tetracyclines are effective in tularemia, streptomycin is usually preferred. They can also be used in infection due to *H. influenzae*, but combination of chloramphenicol with streptomycin is considered to be better.

(vii) **Venereal diseases:** They are effective in the treatment of gonorrhea, syphilis, and chancroid. However, it is not the therapy of choice.

(viii) **Urinary tract infections:** Use of tetracyclines in urinary tract infection is discussed in Chapter 46. They are not so effective against proteus and pseudomonas infections.

(ix) **Plague:** It is the drug of choice in plague. It is given in large doses (4-6 gm daily) orally during first 48 hours. In serious cases, the drug may be given intravenously.

(x) **Acne vulgaris:** Acne vulgaris (pimples) is a disease mostly of young people. There is inflammation of the pilosebaceous follicles, chiefly of the face and upper trunk with the production of comedones, papules and pustules. The main factors in the pathogenesis of acne are (1) seborrhoea which is androgen dependent; (2) hyperkeratinization of the follicular openings, producing blockage and (3) growth of the bacteria, *Corynebacterium acne* and *staphylococci*. These organisms break down sebum fats into irritant fatty acids. All these three factors need attention.

Mild disease may be treated by local application of an antiseptic cream and a keratolytic agent like tretinoin. Frequent washing of the face with plain soap and water is to be encouraged. Severe acne may need systemic antibiotic therapy. Usually, tetracycline is given in the dose of 250 mg four times a day for a week; this is followed by gradual reduction of the dose to 250 mg daily by the eighth week. Other antibacterial drugs found effective are erythromycin, clindamycin and co-trimoxazole.

In females, the use of estrogens may offer some benefit (See Chapt. 61).

The drug therapy may be supplemented by mechanical removal of comedones using a proper extractor.

(xi) **Miscellaneous:** Other infections which respond to tetracyclines include anthrax, actinomycosis, yaws, relapsing fever and leptospirosis. In all these conditions, penicillin is preferred. The drug is also useful in the treatment of tropical sprue and blind loop syndrome.

Tetracyclines are effective in reducing the severity of the attack of whooping cough when started in the first 14 days of illness. A daily dose of 250 to 500 mg. is given according to age for a period of 7 to 10 days. However, they do not seem to modify the course of the disease. Tetracyclines may also be used in the treatment of meningococcal and other infections in individuals allergic to penicillin. In meningitis, initial intravenous dose of 0.5—1 g. every 12 hours followed by 0.5 g. 6 hourly for 8 to 10 days is recommended. Tetracyclines are also effective in infections due to *vibrio fetus* and in mixed infections like peritonitis.

(xii) **Amoebic dysentery:** Discussed in Chapter 51.

Balantidium coli, a protozoan, causes a disease similar to amoebic dysentery in children. Tetracyclines in the dose of 8-10 mg./kg. thrice daily for 10 days are highly effective.

(xiii) **Diagnostic use:** Tetracyclines get accumulated in certain neoplastic cells and exhibit a brilliant, yellow-gold fluorescence when seen under ultraviolet light. This test has been employed to detect malignant cells in sputum or in gastric lavage from patients suspected of lung or gastric cancer.

CHLORAMPHENICOL

Chloramphenicol is a broad spectrum antibiotic derived originally from *Streptomyces venezuelae*. The commercially available drug, however, is now entirely synthetic. There are four isomers of synthetic chloramphenicol. Only one of them is as active as the natural antibiotic. The other three have 1 per cent or less of the activity of the natural antibiotic.

Chloramphenicol differs from tetracyclines in being a nitrobenzene derivative, (Fig. 44.2). The antibiotic is extremely stable over the pH range of 2 to 9.

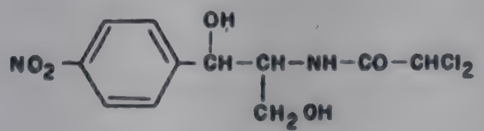


Fig. 44.2: Chloramphenicol

Antibacterial activity: The antibacterial spectrum of chloramphenicol resembles that of tetracyclines. Thus, it is effective against Rickettsia, the chlamydia of the psittacosis-lymphogranuloma group, *Mycoplasma pneumoniae* and against a variety of Gram-negative and Gram-positive organisms. *Salm. typhi*, *H. influenzae* and *H. pertussis* are more susceptible to chloramphenicol than to almost any other antibiotic. The other Gram-negative organisms sensitive to chloramphenicol include

Shigella, *E. coli*, *K. pneumoniae*. *A. aerogenes*, certain strains of *Proteus*, *Pasturella*, *Brucella* and *Vibrio comma*. The bacteroides, some staphylococci resistant to penicillin and a few strains of streptococci are also inhibited. Chloramphenicol is less active against gram positive cocci than penicillin or tetracyclines.

Mechanism of action: Chloramphenicol acts by interfering with the synthesis of bacterial proteins, though in high concentrations, protein synthesis of the host may be affected. Like tetracyclines, it is essentially a bacteriostatic drug. Resistance develops slowly to this antibiotic *in vivo*. However, resistant strains of E. coli, salmonella, shigella and other gram negative bacteria have been reported; it is due to the presence of a specific resistance (R) factor. *E. coli* exhibit a cross resistance to chloramphenicol and tetracyclines.

Absorption, fate and excretion: Unlike tetracyclines, chloramphenicol is completely absorbed from the gut and is better diffusible into the tissues. It gives blood levels as good after oral as after intravenous administration. Being poorly water soluble, its absorption depends to a great extent on particle size. Preparations containing large particles may give blood levels only ¼ to ½ of those obtained from small particles. After oral administration, peak plasma levels are reached within 2 hours and it has a half-life of 1½-3½ hours. A 6 hourly administration of the drug is advocated to maintain a steady therapeutic level. The drug is found in effective concentrations in the pleural fluid and the bile and it reaches the cerebrospinal fluid in about half the blood concentration. Chloramphenicol is also secreted in milk and crosses the placental barrier. Being lipid soluble, chloramphenicol concentrates in the brain, giving levels nine times that in the blood. Given intravenously, the peak blood level is attained immediately but intramuscularly its absorption appears to be much slower than from the gut, mostly due to failure of the salt to hydrolyse.

Chloramphenicol palmitate, the pediatric oral preparation, is inactive *in vitro*, but *in vivo*, it is slowly hydrolyzed by pancreatic lipases in the duodenum, which release free chloramphenicol for absorption.

Chloramphenicol is largely inactivated by hepatic conjugation to glucuronide and is excreted rapidly in the urine. It should be noted that chloramphenicol, a drug that is inactivated entirely in the liver, is excreted only slightly in the bile. The greater part of urinary excretion takes place within first 6 hours. Approximately 80 to 90% of an orally administered dose can be recovered in urine. Nearly 9|10th of the drug is excreted as the inactive form by glomerular filtration and tubular secretion and less than 1|10th is present in the active form which is excreted only by glomerular filtration. The proportion of the active form, however, is high enough to achieve therapeutic concentrations in the urine. Because of the mode of its biotransformation, chloramphenicol can be relatively safely administered in patients with renal impairment but not in those with hepatic insufficiency.

Adverse reactions:

(a) **Intolerance:** This is relatively uncommon. However, skin rashes, drug fever, angioneurotic edema, exfoliative dermatitis, atrophic glossitis and hemorrhages involving the skin, the gastrointestinal tract and the bladder have been reported after chloramphenicol therapy. Herxheimer reaction may develop occasionally following treatment of typhoid and syphilis with chloramphenicol.

(b) **Bone marrow:** The nitrobenzene radical of chloramphenicol may contribute to its bone marrow toxicity; similar bone marrow toxicity can also occur with analogues of chloramphenicol without the nitrogroup. It is probably an allergic reaction characterised by anemia, leukopenia, thrombocytopenia, agranulocytosis and aplastic anemia with pancytopenia. Aplastic anemia has been reported in all age groups. The incidence of this complication is estimated to be between 1:10,000 to 1:100,000. Unduly prolonged treatment and repeated courses with large doses appear to be more likely to cause this complication, although cases of aplastic anemia on ingestion of a few grammes of the drug and even after its prolonged intraocular instillation have been reported. Recent reports suggest that many patients may develop less pronounced hemopoietic changes which are reversible and which, in most cases remain unrecognised; in some cases, the onset of clinical manifestations may be delayed for 2 to 6 months after treatment. Thus, menorrhagia or gastrointestinal hemorrhage occurring several months after the course of treatment may be the first indication of aplastic anemia.

To prevent the deadly complication of aplastic anemia, indiscriminate, prolonged or repeated use of the drug, particularly in children and in those with hepatic insufficiency, should be avoided; peripheral blood smears should be examined at least twice weekly during therapy. The treatment should be stopped if the total leukocyte count drops below 4000 c.mm. or when the proportion of granulocytes is reduced below 40 per cent.

Stoppage of chloramphenicol after the development of aplastic anemia does not prevent the relentless progress of this disorder. It may be noted that administration of phenylalanine along with chloramphenicol has been shown to reduce certain erythroid changes. However, its importance in the prevention of chloramphenicol bone marrow toxicity in man needs confirmation.

(c) **Gray baby syndrome:** This is another dangerous complication of chloramphenicol therapy with a high mortality rate, observed in neonates and infants. It develops when the dose of chloramphenicol is allowed to exceed 100 mg. per kg. body weight per day.

The clinical manifestations appear within 2 to 9 days following the first dose of chloramphenicol. The initial manifestations are vomiting, lethargy, anorexia, abdominal distension and shallow irregular respiration. After 24 hours, the condition develops further, leading to hypothermia, flaccidity, peripheral vascular collapse, gray cyanosis, shock and finally death. The factors incriminated are (i) the deficient conjugation of chloramphenicol in the liver. A low level of hepatic glucoronyl transferase enzyme activity in the first 2 or 3 weeks of life has been demonstrated; and (ii) immaturity of the renal tubules in the infant leading to impairment of excretion of the free form of the antibiotic. To avoid this toxicity, chloramphenicol should be used in infants only when absolutely essential, the dose in infants below 1 month should not exceed 25 mg. per kg. and they should be carefully watched for early signs of toxicity like anorexia, lethargy and abdominal distension.

(d) **Superinfection** can occur during chloramphenicol therapy though it is uncommon as the drug is almost completely absorbed from the gastrointestinal tract.

(e) **Miscellaneous:** Liver damage with chloramphenicol is rare. A 'typhoid shock' syndrome may develop in patients having typhoid fever, on administration of a large loading dose. It is attributed to excessive release of endotoxin from the micro-organisms.

Use of chloramphenicol may result in peripheral neuritis, headache, internal ophthalmoplegia, mental confusion, depression and delirium. Optic neuritis, probably secondary to drug induced pyridoxine deficiency, may occur with the use of this antibiotic. It may also affect the cochlear function if used extensively and repeatedly in the treatment of otitis externa, otitis media and post-operatively following tympanomastoid and fenestration operations.

Chloramphenicol may increase the toxicity of phenytoin in epilepsy and may cause hypoglycemia in diabetics on tolbutamide therapy.

Preparations and dosage:

(i) Chloramphenicol I.P. occurs as fine white needle like crystals or elongated plates. It has a bitter taste and is sparingly soluble in water. It is available as 250 mg. capsules for oral use. Dose: adults, 1 to 3 g. daily in divided doses. For children, 25 to 50 mg. per kg. daily in divided doses.

(ii) Chloramphenicol palmitate oral suspension contains 125 mg. of chloramphenicol base in each 4 ml. of the suspension. The preparation is tasteless and, therefore, employed orally for pediatric use.

(iii) Chloramphenicol monostearoylglycolate, used in the form of a dry syrup, is claimed to give higher blood levels than the palmitate ester.

(iv) Chloramphenicol sodium succinate has a high aqueous solubility in comparison to chloramphenicol base and is, therefore, the agent of choice for parenteral chloramphenicol therapy. Repeated use causes local irritation. A 10% solution is administered subcutaneously. A 25 to 40 per cent solution is used intramuscularly while a 10 per cent solution is injected slowly by intravenous route or administered through a saline drip. The doses are similar to those given orally.

(v) Chloramphenicol ophthalmic ointment contains 1 per cent of the drug. Buffered eye drops containing 0.5 per cent of the drug are available.

Therapeutic uses: Chloramphenicol can be used for similar purposes as tetracyclines but its use should primarily be restricted to the treatment of infections caused by *S. typhi* and *paratyphi* group of organisms. Because of its bone marrow toxicity, it should not be employed primarily as a broad spectrum antibiotic. The major therapeutic indications for chloramphenicol are:

(i) **Typhoid fever:** Chloramphenicol is the drug of choice in the treatment of this condition. For best results, early administration is desirable. It is given orally in the dose of 50 mg. per kg. daily (about 2 g. in adults) in 3 or 4 divided doses until the temperature is normal. The dose may then be reduced to 30 mg. per kg. per day. Chloramphenicol therapy with this dose should be continued for a period of 12-14 days. It is important to avoid an initial loading dose as the patient may develop 'typhoid shock syndrome.' In an acutely ill patient, the first few doses of chloramphenicol may be administered by intramuscular or intravenous injection. In children, a dose of 25 to 50 mg. per kg. per day is recommended.

After institution of therapy, apparent clinical improvement is seen within 48 to 72 hours. Temperature returns to normal within 3 to 5 days. Clinical cure is thus achieved before the gastrointestinal ulcerations have healed and hemorrhage and perforation may occur during chloramphenicol therapy even in an afebrile patient. It is desirable, therefore, to advise complete bed rest for a period of 2 to 3 weeks to allow sufficient time for healing of the ulcerated bowel.

The relapse rate in patients treated with chloramphenicol therapy is significantly higher than in untreated cases. Relapses, however, are amenable to similar treatment. They are probably due to chloramphenicol induced suppression of antibody formation and its bacteriostatic action. Prolonged treatment, however, carries the risk of hemopoietic toxicity. Another measure suggested to prevent relapse is the administration of T.A.B. vaccine at the end of the course of chloramphenicol. The efficacy of this method, however, needs confirmation.

Trimethoprim-sulphamethoxazole combination (co-trimoxazole) is also effective in typhoid fever. The dose recommended is 2 tablets twice a day continued until seven days after defervescence. The response is claimed to be superior to that to chloramphenicol therapy. Since it is bactericidal in effect, the subsequent relapse rate or carrier state is likely to be uncommon. The combination is particularly useful in patients with organisms resistant to chloramphenicol.

Ampicillin and furazolidone have also been used to treat typhoid fever. The therapeutic response, however, is slower in onset and often inadequate.

The glucocorticoids, when employed in conjunction with appropriate antimicrobial therapy shorten the duration of pyrexia but do not otherwise affect the outcome, and may even enhance chloramphenicol induced depression of the immune response. Their routine use, therefore, is unnecessary and not recommended. But they are beneficial in the treatment of 'typhoid shock' occurring either as a result of chloramphenicol therapy or during the natural course of the disease. Glucocorticoids have also been reported to be useful in occasional cases of enteric fever without suppurative complications that do not respond to chloramphenicol after 6 to 8 days of therapy. The preparation used is prednisolone, given in the dose of 40 mg. in 4 divided portions on the first day, 30 mg. on the 2nd day and 20 mg. subsequently. Treatment should be given for a total period of 5-6 days and withdrawal should be gradual and tapering; an earlier cessation may result in a sharp recurrence of pyrexia and symptoms.

Patients with typhoid fever are unusually sensitive to the action of salicylates and may develop profound hypothermia with the use of these agents, even in small doses. Tepid sponging should be used instead of salicylates for reducing fever. Irritant purgatives are contraindicated for fear of causing hemorrhage or perforation.

Treatment of carriers: Chloramphenicol, being a bacteriostatic agent, does not affect the incidence and duration of typhoid carrier state. It is, therefore, necessary to obtain 6 consecutive negative cultures for salmonella from stool and urine at 2-3 days intervals before permitting the patient's release from isolation. Ampicillin, administrated in a total daily dose of 6 g., along with 2 g. of probenecid daily, for a period of 3 months has been successfully employed for terminating the carrier state in patients without gall stones and a normal gall bladder function. Co-trimoxazole has also been reported to be effective when used in the dose of 2 tablets twice a day for 3-6 months.

Paratyphoid fever, though usually a milder disease, needs similar treatment as typhoid fever.

(ii) **Urinary tract infections:** Infections due to *Proteus*, *Aerobacter*, *K. pneumoniae*, *Pseudomonas aeruginosa* and *H. influenzae*, refractory to other chemotherapeutic agents, may respond to chloramphenicol. It is, however, not the drug of choice.

(iii) **H. influenzae meningitis:** Chloramphenicol, in the daily dose of 4 g. for 2 weeks, was considered formerly the drug of choice in the treatment of this condition. It was often combined with sulfonamides. However, other agents including sulfonamide-streptomycin combination, tetracyclines or ampicillin are found to be equally or more effective and much less toxic.

(iv) **Plague:** It is effective in large doses, 50-75 mg./kg. body weight daily.

(v) **Miscellaneous:** Because of its satisfactory penetration into the intraocular fluid on local and systemic administration as compared to penicillin and tetracyclines, chloramphenicol is widely employed in the treatment of Gram-positive ocular infections and is also useful in trachoma. It is also used in chronic otorrhea, particularly due to Gram-negative organisms and in skin infections. In patients who are allergic to penicillin, chloramphenicol, 1 g. four times a day for 10-12 days is an effective alternative in meningococcal infections.

In whooping cough, chloramphenicol serves the same purpose as tetracyclines. Even though effective against the rickettsiae, chloramphenicol is not preferred in these infections because of its toxicity. It may, however, be effectively used in brucellosis in tetracycline resistant or hypersensitive cases in the dose of 0.75 to 1 g. at 6 hourly intervals.

The combination of chloramphenicol and kanamycin is very effective in gram negative septicemia except that due to pseudomonas.

PHARMACOTHERAPY OF BACILLARY DYSENTERY

Bacillary dysentery or shigellosis is usually a self-limited acute illness characterized by diarrhoea with blood and mucus in the feces, tenesmus, fever, intestinal colic and tenderness. Nausea and vomiting may occur to a variable degree. In many patients, the illness is characteristically short, for 12-24 hours, followed by constipation and needs only symptomatic treatment. The infection is usually localised to the gastrointestinal tract but pneumonitis is not infrequent in children and bacteremia may occur occasionally. *Shigella shiga* infection is often more severe than that due to other strains.

Specific treatment: Sulfonamides are highly effective in the treatment of shigellosis but in many places where the infection is endemic, a large proportion of the bacilli have developed resistance to sulfonamides. The systemically acting sulfonamides like sulfadiazine and sulfafurazole are preferred to the locally acting preparations like phthalyl or succinylsulfathiazole. This is because of the ability of the absorbable sulfonamides to reach the organisms actively multiplying in the submucous layer of the bowel wall. Sulfonamides usually control the infection within 24 to 48 hours. Acute form responds better than chronic form and Shiga and Flexner infections are better controlled than Sonnei infections. The treatment is usually continued for a week but in Sonnei infection, it should be given for 10 to 14 days.

Tetracyclines are effective in obtaining bacteriological cure in sulfonamide allergic or resistant cases and do so with small doses. They, however, should be used with caution in hospitals for the fear of precipitating a superinfection. They are administered initially in the dose of 500 mg. 6 hourly followed by 250 mg. at 6 hourly intervals. For children, a dose of 50 to 60 mg. per kg. is recommended. Treatment should be continued for a minimum period of 5 days or if possible, till the stool culture is negative on 3 successive days. Bacterial resistance to tetracyclines has been reported. Ampicillin is also effective in similar doses. Chloramphenicol used in the dose of 250 mg. 6 hourly, also cures the infection but does not appear to have any advantage over tetracyclines except that it is cheaper. It must be emphasized that spontaneous clearance of stools is known to occur over a period of weeks irrespective of whether or not the patient has received antibacterial treatment. Because of the distinct risk of transference of multiple antibiotic resistance factors from Shigella species to other more dangerous pathogens, it is advisable to use chemical (Sulfonamides and Furazolidone) rather than antibiotic drugs to treat such cases. Only in patients with life threatening dysentery, the use of antibiotics is probably justified and should be guided by accurate knowledge of the enterobacteria involved. Other drugs like streptomycin, paramomycin, neomycin and kanamycin given orally are also effective but are not recommended for routine therapy.

Adjuvant treatment: This consists of (1) treatment of diarrhoea (see Chapter 36), and (2) correction of fluid and electrolytic imbalance. In severe cases, the patient should receive intravenous fluids in addition to oral feeding. With recovery, liquids and easily digestible food should be administered by mouth. In the post-diarrhoeal phase, the patient's constipation should not be interfered with because it represents the body's effort to splint the bowel and it usually clears up within 3 days.

PHARMACOTHERAPY OF CHRONIC BRONCHITIS

Chronic bronchitis is a symptom complex characterised by cough with production of sputum, in the absence of an obvious cause such as acute inflammatory or neoplastic disease of the lung or bronchiectasis. In many elderly patients, it is progressive and incurable, terminating eventually in right heart failure.

Pharmacotherapy of chronic bronchitis is primarily directed towards the infection as it is controllable. The pathological changes which develop in the lung, such as emphysema, however, are irreversible.

The treatment can be divided into (I) treatment of exacerbations and (II) management of the chronic state.

(I) **Treatment of exacerbations:**

(a) *Antimicrobial therapy*: Patients with chronic bronchitis are extremely susceptible to acute attacks. Such attacks usually develop during the monsoon months in India and during the winter in the Western countries. During such attacks the sputum becomes purulent. The commonest pathogens involved are *H. influenzae* and *D. pneumoniae* although *Staph. aureus* or *K. pneumoniae* are not infrequent.

Sputum cultures and bacterial sensitivity tests should preferably be carried out before institution of therapy but in severe cases, one need not wait for the results before instituting treatment. The antibiotic regimens recommended are (i) 0.5 to 1 mega unit of benzylpenicillin along with 0.5 to 1 g. of streptomycin intramuscularly twice daily, (ii) tetracycline 1 to 2 g. daily by mouth in divided doses, (iii) ampicillin, 0.25 to 0.5 g. 4 times daily by mouth, (iv) chloramphenicol initially in the dose of 500 mg. thrice daily for 2 days followed by 250 mg. thrice daily, or (v) sulfamethoxazole (1600 mg.) trimethoprim (320 mg.) combination, daily in divided doses. All these regimens are equally effective and any one may be selected according to the convenience.

Antimicrobial therapy should be continued for at least 7-10 days. Streptomycin-penicillin therapy is obviously more suitable for hospitals while the other regimens are convenient for domicilliary practice. If the patient fails to respond satisfactorily, bacteriological examination of the sputum is indicated and an appropriate change in the antibiotic therapy should be made. Prompt institution of antibacterial treatment at the beginning of illness minimises further bronchopulmonary damage.

(b) *Control of symptoms*: Bronchodilators effectively counter the respiratory distress due to mucosal swelling. If the asthmatic element is prominent, corticosteroids may have to be employed. For liquefaction of thick and sticky secretions, various mucolytic agents have been employed; their usefulness, however, is doubtful. Expectorants may however be employed to facilitate the expulsion of secretions. If the patient is expectorating large quantities of sputum, postural coughing may prove beneficial.

In severe respiratory distress with hypoxia and hypercapnia, oxygen has to be given intermittently. The administration of oxygen removes the hypoxic stimulus to the respiratory centre and thus, further increases the carbon dioxide retention. The patient therefore, should be closely observed to determine whether he is improving or becoming more stuporous with oxygen therapy.

(ii) **Management of chronic state:** Prophylactic therapy with 1 g. of tetracycline or ampicillin daily is sometimes recommended during periods predisposing to respiratory infection. Such long term therapy is expensive and it is highly questionable whether it has any particular benefit over intermittent therapy started at the first sign of an exacerbation. It is, however, important to avoid all irritants to the respiratory tract, especially smoking. Breathing exercises are highly beneficial and patients should be trained to take such exercises at home.

ANTIFUNGAL ANTIBIOTICS

Fungal infections are common, not only as primary diseases, but also secondary to therapy with oral antibiotics. Individuals suffering from malignancy, diabetes mellitus and those on corticosteroids are more prone to develop fungal infections.

In general, the antibacterial antibiotics have little effect on fungal infections. An exception to this statement are infections like actinomycosis which responds to penicillin and tetracyclines, and nocardiasis which responds to sulfonamides and streptomycin.

The antifungal antibiotics are:

I. **Those employed locally,** such as nystatin and other polyene antibiotics like candicidin, pimaricin, hamycin and tricomycin.

II. Those used systemically, such as griseofulvin and amphotericin B.

I. Antibiotics employed locally:

NYSTATIN (Mycostatin): This antibiotic, obtained from *Streptomyces noursei*, contains many double bonds in its chemical structure and hence, is called a polyene antibiotic. It is a pale yellow, water-insoluble substance, stable for several months in dry state at 4°C; it rapidly loses its activity in the presence of water or plasma.

Antifungal activity: Nystatin shows inhibitory activity against several fungi *in vitro; Candida, Histoplasma, Blastomycoses, Trichophyton* and *Microsporum audouini* are sensitive. It has no antibacterial activity. It is also not absorbed from the gut, the skin or mucous membrane. On parenteral administration it produces a variety of toxic effects including nephrotoxicity and its activity is reduced in the presence of plasma. Hence, its use is restricted to the treatment of localised infections, mainly those caused by *candida*. Resistance does not readily develop to this antibiotic *in vivo*.

The exact mechanism of action of this antibiotic is not understood. Depending upon concentration, it can act either as a fungistatic or a fungicidal agent. It combines with the cell membrane of the yeast and interferes with vital cellular processes like respiration and glucose utilisation.

Adverse reactions: Adverse effects encountered with nystatin used locally are usually mild. Oral administration may cause nausea, vomiting and diarrhoea.

Preparations and dosage: Nystatin tablet N.F. contains 500,000 units of nystatin. Dose: 500,000 units 8 hourly in adults and in children over 6 years, 100,000 units 2 to 3 times daily for infants, and 200,000 units 2 to 3 times for those between 1 to 5 years.

(ii) Nystatin suspension N.F. contains 100,000 units of nystatin per gram. Oral topical application is usually made 3 times a day.

(iii) Nystatin pessary or vaginal tablet N.F. contains 100,000 units of nystatin. The pessary is inserted in vagina twice or thrice daily.

(iv) Nystatin ointment contains 100,000 units of nystatin per gram. An ointment containing nystatin and neomycin is also available.

Therapeutic uses: Nystatin is effective in the treatment of localized candidiasis of vagina, mouth, skin and the gastrointestinal tract. Nail involvement due to candida is not benefited.

Monilial infection of the vagina responds to the insertion of 100,000 units twice daily for a minimum period of 2 weeks. It may be necessary to repeat the treatment if a relapse occurs. Treatment of monilial vaginitis in pregnant patients reduces the possibility of thrush in the newborn. For the latter, a suspension containing 100,000 units of the antibiotic is dropped into the infant's mouth 4 times daily. The treatment should be continued for a prolonged period after all clinical lesions have subsided. For intestinal candidiasis, 500,000 units 8 hourly is the adult dose. Doses in infants and children have been mentioned previously.

PIMARICIN: This antibiotic, obtained from *Streptomyces notalensis*, shows a marked activity against *Aspergillus fumigatus, Trichophyton violaceum* and *Trichomonas vaginalis.* It is mainly fungicidal. The antibiotic is not absorbed orally and is too toxic for parenteral use. A single oral dose of 400 mg. may be given for oral aspergillosis while a 2.5 per cent suspension may be used for inhalation in bronchopulmonary aspergillosis and candidiasis. Ophthalmic ointment (5%) is used to treat keratitis due to species of fusarium and Cephalosporium.

HAMYCIN: It is a polyene antibiotic obtained from *Streptomyces pimprina* recovered from local soil in the Research Laboratories of Hindustan Antibiotics, India. It is claimed to be highly effective in *cryptococcosis, blastomycosis, histoplas-*

mosis, *coccidiodomycosis* and *candidiasis*. Unlike nystatin, its antifungal activity is enhanced in the presence of serum. Orally, it has been used to treat B. dermatitidis and blastomycosis in man. The dose recommended is 10-20 mg/kg daily.

The adverse effects include diarrhoea, elevation of SGOT levels, eosinophillia, and nephrotoxicity.

Hamycin suspension (oral application) N.F. contains 140,000 units of hamycin.

Local treatment for 10 to 14 days has been found effective in vaginal candidiasis and in thrush. Some workers claim that the drug is indistinguishable from trichomycin.

Trichomycin and **Candicidin** are other polyene antibiotics which are used locally in the treatment of vaginitis due to trichomonas and candida.

II. Antibiotics employed systemically:

GRISEOFULVIN (Grisovin): Griseofulvin, isolated from *Penicillium griseofulvium* is the first chemical compound to cure effectively infections due to the superficial dermatophytes (ring worm), when administered orally. It is an odourless, white thermostable substance, stable at room temperature and relatively insoluble in water.

Antifungal activity: *In vitro*, the antibiotic inhibits the growth of various species of *Trichophyton*, *Microsporum* and *Epidermophyton*. It is not effective against bacteria, *C. albicans*, or any of the deep fungi. The antibiotic is mainly fungistatic. Development of resistance by the susceptible fungi has not been shown *in vivo*.

The mechanism of action of griseofulvin is uncertain. The antibiotic exhibits mild *cytotoxic* properties similar to colchicine and has also a weak anti-inflammatory effect. It mainly acts on the growing fungal cells. Experimental evidence suggests that it probably acts as a purine analogue and interferes with nucleic acid synthesis.

Absorption, fate and excretion: Oral administration of a maximum single dose produces peak plasma levels within 4 hours. Small particles are better absorbed than large particles, divided doses achieve higher blood level than a single oral dose and a diet rich in fat enhances the drug absorption. Very small amounts are excreted in urine while large amounts are eliminated in unchanged form in the feces. The drug is deposited in keratin precursor cells and gets firmly incorporated in keratin, making it resistant to fungal invasions. The antibiotic exhibits greater affinity for the diseased than the normal skin.

Adverse reactions: These are usually mild and include headache, epigastric distress, nausea, vomiting and diarrhoea.

Allergic and photosensitivity reactions can occur. Since griseofulvin is derived from a species of penicillium, the possibility of cross allergy with penicillin exists.

The nervous system disturbances include paraesthesiae, peripheral neuritis, vertigo, psychomotor incoordination, lethargy and fatigue with paradoxical insomnia and blurring of vision. Other adverse effects include transient leukopenia, proteinuria, gynacomastia, pigmentation of the genitalia and an increase in urinary coproporphyrin and/or protoporphyrin levels; these are, however, very rare. Griseofulvin may depress the anticoagulant activity of warfarin and may occasionally elicit an antabuse-like reaction after ingestion of alcohol. Superinfection with *C. albicans* has been reported. Simultaneous administration of griseofulvin and phenobarbitone may retard the absorption of the latter from the gastro-intestinal tract.

Preparations and dosage: The adult dose is 500 mg. daily in 2 or 4 divided doses. In certain infections like tinea capitis a larger dose of 1.5 g. daily may be necessary. Children are given 10 mg. per kg. daily, administered as a single dose or in divided doses.

Therapeutic uses: Griseofulvin has made possible clinical control of some chronic resistant ring worm infections and has shortened the duration of treatment in others. Nevertheless, the narrow spectrum and the high cost of griseofulvin therapy demand that it should not be used routinely unless the much cheaper and well established topical therapy has been adequately tried. The indications are:

(i) Tinea capitis (ringworm of the scalp) where clinical cure usually occurs within 4 to 6 weeks of therapy.

(ii) Tinea barbae (fungus infection of the beard caused by T. faviforme, T. mentagrophytes and M. canis).

(iii) Tinea cruris and tinea corporis (ringworm of the groin and the body).

(iv) Tinea pedis and tinea manus (ringworm of the feet and hands). Griseofulvin is more effective in chronic fungal infections at these sites than in the acutely inflamed or macerated forms. In all above conditions the treatment is continued for 4 to 8 weeks.

(v) Onychomycosis (Fungus infection of the nails): Treatment with griseofulvin is more successful for fingernails than toenails which may respond minimally or not at all. Treatment for infection of the fingernails is given for 4 to 6 months, while an infection of the toenails is treated for 6 to 12 months. Since chronic fungal infections tend to cause hyperkeratosis, concomitant topical keratolytic therapy with salicylic acid is necessary in majority of the cases.

AMPHOTERICIN B (*Fungizone*): This polyene antibiotic, obtained from *Streptomyces nodosus*, is a yellowish powder relatively insoluble in water.

Antifungal activity: Amphotericin B has a wide antifungal activity. It inhibits the growth of *Histoplasma capsulatum*, *Cryptococcus neoformans*, *Sporotrichum schenckii*, *Coccidoides immitis* and *Blastomycoses brasiliensis* in low concentrations. Candida responds to a slightly higher concentration. Depending upon the concentration, it can be fungistatic or fungicidal Candida may develop resistance to this antibiotic *in vivo* and a cross resistance with nystatin may be seen which argues for a probably similar mechanism of action of these two antibiotics.

Absorption, fate and excretion: Amphotericin B is poorly absorbed from the gut and on topical application. The intramuscular administration is painful. The drug, therefore, is given intravenously in the treatment of systemic infections.

On intravenous administration of a therapeutic dose, only 5 per cent of the drug is found in urine within 24 hours. The drug does not achieve a satisfactory concentration in the CSF. The metabolic fate of the antibiotic is unknown. Very little drug appears in the urine.

Adverse reactions: Amphotericin B is a highly toxic antibiotic and a variety of reactions may develop after its intravenous use. These include phlebitis at the site of injection, nausea, anorexia, vomiting and profound generalized malaise. Other effects like chills, fever, flushing, headache, anaphylactic reactions, skin rash, diplopia, vertigo, convulsions, myalgia and peripheral neuritis are also seen. Intrathecal administration of the drug may result in arachnoiditis. The drug can cause hemorrhagic gastroenteritis, anemia and thrombocytopenia. Acute hepatic failure with jaundice and hepatocellular dysfunction are provoked in some cases. Hypotension, ventricular failure and cardiac arrest may develop rarely. Nearly 3/4ths of the patients on amphotericin B develop impairment of renal function as manifested by increased blood urea nitrogen and nonprotein nitrogen levels, hypokalemia, appearance of urinary casts and sometimes microscopic hematuria. Irreversible renal damage may occur when the total dosage exceed 5 g. Superinfection with bacteria may occur.

Preparations and dosage:

(i) Amphotericin B lotion contains 3 per cent of the antibiotic. It is applied topically twice or thrice daily.

(ii) Amphotericin B intravenous: A concentration of 0.1 mg./ml. in 5 per cent dextrose should be used. Sodium chloride solution or other bacteriostatic agents precipitate the drug. Therapy is initiated with a dose of 0.05 mg. per kg. The total dose is given over 6-12 hour period. It is then increased daily by 5 to 10 mg., until a dose of 1 mg./kg. is reached. This is continued on alternate days. In severe cases, a maximum dose of 1.5 mg. per kg. may be given on alternate days. The intrathecal dose of the drug is 0.5 mg.

Therapeutic uses: Topically, the antibiotic is useful in the treatment of candida lesions.

For systemic therapy, the patient should be hospitalized. A course of treatment should not be embarked upon unless the diagnosis is certain and the disease has an unfavourable prognosis. This is the only antibiotic available at present for serious systemic fungal infections and, though toxic, could be life saving in some cases.

Intravenous amphotericin B is the treatment of choice in the primary, cutaneous and disseminated forms of North American blastomycosis, South American blastomycosis, histoplasmosis, cryptococcosis, candidiasis, sporotrichosis, aspergillosis, chromoblastomycosis and occasionally in phycomycosis and maduromycosis. It may be administered intrathecally in fungal meningitis that does not respond to intravenous therapy. The cure rate is 80 to 90 per cent in majority of the conditions except coccidiodomycosis.

SARAMYCETIN (X-5079 C) is a peptide antifungal antibiotic, claimed to be useful in systemic fungal infection. It is better tolerated than amphotericin B. It is not so useful in coccidiodomycosis, cryptococcosis and severe candida infections. The drug is under evaluation.

5-FLUOROCYTOSINE: This is a non-antibiotic synthetic fluorinated pyrimidine discussed here as it is useful in systemic fungal infections. Given orally, it is well absorbed and reaches adequate concentration in blood and CSF. It is almost entirely excreted unchanged by glomerular filtration. The drug appears to be useful in cryptococcal meningitis and systemic candidiasis. Adverse reactions include G.I. disturbances, liver damage and bone marrow depression. However, it is less toxic than amphotericin B. It is administered in the daily dose of 50-150 mg/kg body wt. given at 6 hour intervals.

45 General Principles of Chemotherapy of Infections

Many therapeutically effective antibiotics are now available and more are being added to this list. It is necessary, therefore, to have certain guiding principles in planning a chemotherapeutic regimen for an individual patient.

Selection of antimicrobial agent: This will be decided by:

(1) *Clinical diagnosis* regarding the etiology and the clinical course of the infection. One must decide whether the given illness is likely to be due to a microorganism susceptible to one of the available antibiotics. Antibiotics are not nonspecific antipyretics and their use for all and sundry cases of fever is to be deprecated. It should also be appreciated that many cases of fever such as due to common cold are due to viruses which are not susceptible to antibiotics. Use of antibiotics in such cases, except under special circumstances, is not justified.

(2) *Identification of the causative microorganism* and study of its sensitivity to antimicrobial drugs. This, however, may not always be possible owing to lack of adequate facilities.

(3) *Nature of the drug,* bacteriostatic or bactericidal. Bactericidal drugs are usually preferred to bacteriostatic agents. Carriers should be treated with bactericidal drugs since bacteriostatic agents are not so effective in the absence of inflammation (Table 45.1).

Table 45.1: **Commonly used bacteriostatic and bactericidal drugs**

Bactericidal	Bacteriostatic
Penicillin	Sulfonamides
Streptomycin	Nitrofurans
Polymyxin, colistin	Erythromycin
Kanamycin	Tetracyclines
Neomycin	Chloramphenicol
Cephalosporins	Lincomycin
Bacitracin	Triacetyloleandomycin
Isoniazid	Novobiocin
Gentamicin	PAS

(4) *Severity of the disease* and general condition of the patient. Thus, a mild case of bacillary dysentery in an otherwise healthy individual will usually respond satisfactorily to sulfonamide therapy, while in severe cases, tetracyclines or chloramphenicol may be necessary.

(5) *Risk of toxicity* of the drug, particularly in the presence of liver or kidney damage. The risk involved in using a more toxic drug in preference to less effective but less toxic agent is justified only if the infection is severe.

(6) *Age of the patient*: Certain drugs like chloramphenicol may cause serious toxic effects in infants in whom liver enzymes and renal function are not adequately developed.

(7) *Possibility of drug resistance* e.g. if the infection is due to Staphylococci suspected to be resistant to penicillin, another antibiotic will have to be used.

(8) *History of previous allergic reaction* or intolerance to the antimicrobial agent and

(9) *The cost of therapy*: This is particularly important where many equally effective drugs are available for a given infection. An antibiotic should not be selected simply because it is 'the latest'. Newer drugs are always costly and not necessarily better than older ones.

Although bacterial sensitivity tests give important information, they are neither necessary nor practicable in daily practice. Sometimes, they can even be misleading and hence, the physician should use his clinical judgement in selecting an antibiotic and not depend blindly on the results of such tests. It must be realised that the organisms isolated by the bacteriologist may not be the prime cause of the disease under treatment. This is particularly so in case of organisms cultured from sputum and feces. Similarly, the sensitivity data obtained from *in vitro* studies does not necessarily hold true *in vivo*. Bacterial sensitivity tests, however, are useful in selecting a proper regimen in chronic cases like respiratory or urinary tract infections, resistant Staphylococcal infections and chronic osteomyelitis.

Certain antimicrobial drugs are cleared from the blood by mechanisms not involving the kidneys. Drugs in this group are erythromycin, chloramphenicol and doxycycline and rifampicin. These drugs are metabolised to inactive products and although these metabolic products accumulate in the presence of renal failure, they are not so dangerous to the patient. In contrast to this, antibacterial drugs like streptomycin, polymyxins, kanamycin, gentamicin, vancomycin, colistin, probably amphotericin B, nitrofurantoin and P. A. S. which are removed almost entirely by the kidney, accumulate in the blood in the active form in patients with renal function below 25 per cent of normal. Majority of these agents are highly effective against Gram negative organisms but are also capable of producing nephrotoxic and neurotoxic effects. If these drugs are to be used in the presence of renal failure, they must be used in reduced doses, as guided by the blood urea or creatinine levels. The 'loading dose' remains the same as the 'usual' initial dose in a person with normal renal function. Subsequently, half of this dose is given as the maintenance dose at intervals equal to the calculated or expected half-life of the drug. Table 45.2 shows the guidelines for the use of these antibiotics in patients with renal failure.

Antibiotics like ampicillin, cloxacillin, carbenicillin, other penicillins in general, and cephaloridine can be used safely but need reduction in dosage, in patients with chronic renal failure. Large doses of cephaloridine, however, may cause acute oliguria. The tetracyclines increase protein catabolism. Further, accumulation of protein metabolites in the already uraemic patient would make the condition worse. In addition, the disturbance in protein metabolism may result in liver failure. It is advisable, therefore, to avoid tetracyclines (except doxycycline) in uraemic patients.

Sulfadimidine or sulfadiazine could be used in the presence of mild renal failure but should be avoided in moderate or marked impairment of renal function.

Table 45.2: **Doses of Antimicrobial Agents in Renal Failure

Agent	Loading dose	Maintenance dose	Interval between doses	
			*Oliguria	†Azotemia
Gentamicin	2 mg./kg.	1 mg./kg.	2-3 days	1 day
Kanamycin sulfate	15 mg./kg.	7.5 mg./kg.	3-4 days	2 days
Streptomycin	15 mg./kg.	7.5 mg./kg.	3-4 days	2 days
Colistimethate sodium	5 mg./kg.	2.5 mg./kg.	3-4 days	2 days
Polymyxin B sulfate	2.5 mg./kg.	1.25 mg./kg.	3-4 days	2 days
Tetracycline	0.5 gm.	0.25 gm.	3-4 days	2 days
Chloramphenicol	0.5 gm.	0.5 gm.‡	6 hours	6 hours
Ampicillin	0.5 gm.	0.25 gm.	12 hours	6 hours
Cephalothin sodium	1.0-2.0 gm.	0.5-1.0 gm.	24 hours	12 hours

* Creatinine clearance 10 ml. per minute or less.

† Creatinine clearance more than 10 ml. per minute.

‡ Reduce the dose in patients with severe liver disease.

** Barnett, J. A. and Sanford, J. P.: J.A.M.A. 209: 1514, 1969.

The renal excretory mechanisms in neonates and in premature infants are not well developed. Hence, antibiotics which are essentially excreted by the kidney tend to accumulate in such cases, leading to their toxic effects. The doses of these drugs for newborns and premature infants should be reduced and spacing between doses is increased as compared to those advocated for adults.

The plasma half-life of rifampicin, isoniazid, lincomycin and unconjugated chloramphenicol are longer in patients with impaired liver function.

The antimicrobial drug selected should be given in adequate doses for a sufficient period depending upon the type of case.

In majority of the simple acute infections and even in certain chronic conditions, **orally effective**, relatively nontoxic and inexpensive drugs should be preferred. Parenteral therapy with antibiotics is inconvenient to the patient, is more expensive and needs medical supervision. Such therapy, particularly if the drug is potentially toxic, should be reserved for (1) serious cases, (2) patients who cannot take oral therapy or the drugs are not absorbed orally and (3) those where the organisms have developed resistance to orally used routine drugs.

In the management of obstructive lesions, necrotic and pyogenic infections, surgical intervention may be necessary for effecting a complete cure.

Antibiotic combinations: Routine simultaneous use of two or more antimicrobial agents is not recommended. These drugs may, however, be combined under certain circumstances for the following reasons:

(1) *Increasing the potency of antibacterial action*: True antibiotic synergism is rare and the enhanced therapeutic activity observed following certain combinations is usually an additive effect. Penicillin is combined with streptomycin in bacterial endocarditis due to streptococci. Brucellosis responds better to streptomycin-tetracycline combination than to tetracycline alone. Hydrolysis of penicillin G and ampicillin by penicillinase has been shown to be inhibited by simultaneous use of a penicillinase resistant penicillin which acts as penicillinase inhibitor. Thus, administration of penicillin G or ampicillin with cloxacillin may render the resistant organisms more susceptible to penicillin G or ampicillin. A combination of gentamicin with carbenicillin acts synergistically against pseudomonas infection. It should be noted, however that for a given antibiotic combination the dose of the individual antibiotic needed to accomplish synergism varies according to the type of organism.

(2) *In mixed infections with bacteria sensitive to different drugs*: Penicillin is combined with streptomycin in peritonitis.

(3) *To delay the development of resistance* as in chronic infections like tuberculosis, leprosy and chronic bronchitis.

(4) *To decrease the adverse reactions* to an individual drug, another agent may be added so that the doses of each drug can be reduced and possible toxicity avoided.

(5) *When the infection is severe and the body defence is poor* or etiological diagnosis is difficult, combined antimicrobial therapy may be given in order to broaden the spectrum of antibacterial activity. However, in such cases, the appropriate regimen should be instituted once the diagnosis is made.

(6) *For reducing the chances of superinfection*: Long term tetracycline therapy is sometimes combined with antifungal agents to prevent the superinfection due to fungi such as monilia. Unfortunately, not all fungi are eliminated and even when the fungal population is decreased, diarrhoea may persist.

(7) *Reducing the cost of therapy*: Combination of penicillin with sulfonamides may work out cheaper than tetracyclines used alone. Similarly, in case of Gram-negative organisms, combination of streptomycin with a sulfonamide may be cheaper than gentamicin given alone.

It is not possible to predict which combination will have a synergistic effect and

Table 45.3: **Antimicrobial Drugs of Choice**

Organism	Antimicrobial Agents	
	First Choice	Other Effective Drugs
Diplococcus pneumoniae	Penicillin G	Erythromycin, cephalothin, cephaloridine, lincomycin, a tetracycline.
Streptococcus pyogenes	Penicillin G	Same as above.
Streptococcus viridans	Penicillin G alone or + streptomycin	Erythromycin, cephaloridine, lincomycin, vancomycin.
Enterococcus, (*Streptococcus faecalis*)	Penicillin G + streptomycin (or kanamycin) or ampicillin, with or without streptomycin (or kanamycin)	Vancomycin, erythromycin + streptomycin.
Staphylococcus aureus	When bactericidal effect required: penicillin G or V, methicillin or allied drug	Lincomycin, erythromycin, vancomycin, cephalothin, novobiocin, kanamycin, chloramphenicol, a tetracycline.
Neisseria meningitidis (*intracellularis*)	Penicillin G or ampicillin + sulfadiazine	Erythromycin, tetracycline, chloramphenicol.
Neisseria gonorrhoeae	Penicillin G	A tetracycline, erythromycin, spectinomycin, streptomycin.
Treponema pallidum	Penicillin G	A tetracycline, erythromycin.
Fusospirochetes (*Vincent's*)	Penicillin G	Erythromycin, a tetracycline.
Spirillum minus	Penicillin G	Streptomycin, erythromycin, a tetracycline.
Haemophilus influenzae	Ampicillin	Chloramphenicol, a tetracycline, streptomycin, erythromycin, sulfonamide.
Bordetella pertussis	Erythromycin	A tetracycline, chloramphenicol, Ampicillin
Haemophilus ducreyi	Sulfonamide	A tetracycline, chloramphenicol.
Donovan bodies of granuloma inguinale	A tetracycline	A tetracycline + streptomycin, chloramphenicol, ampicillin.
Trachoma	A tetracycline	Sulfonamide, erythromycin.
Mycoplasma	A tetracycline	Erythromycin, chloramphenicol.
Rickettsia	A tetracycline	Chloramphenicol.

Table 45.3: Continued—

Organism	Antimicrobial Agents	
	First Choice	Other Effective Drugs
Corynebacterium	Penicillin G	Erythromycin, a tetracycline.
Clostridia	Penicillin G	Erythromycin, a tetracycline.
Salmonella typhosa	Chloramphenicol	Cotrimoxazole, ampicillin.
Escherichia coli	Co-trimoxazole	Ampicillin, nitrofurantoin, gentamicin, cycloserine.
Klebsiella-Aerobacter	Gentamicin	Cephaloridine, colistin, kanamycin, cotrimoxazole.
Proteus mirabilis	Ampicillin	Kanamycin, cotrimoxazole, chloramphenicol, gentamicin.
Proteus vulgaris	Chloramphenicol + kanamycin	A tetracycline + streptomycin, carbenicillin
Pseudomonas	Carbenicillin + gentamicin	Tobramycin, kanamycin, colistin.
Shigella	Sulfonamide or furazolidine	Ampicillin, streptomycin, neomycin, kanamycin, colistin, chloramphenicol, tetracycline.
Brucella	A tetracycline + streptomycin	Erythromycin, novobiocin, ampicillin.
Pasteurella tularensis	Streptomycin	A tetracycline, chloramphenicol.
Pasteurella pestis	Tetracycline + streptomycin	Chloramphenicol.
Bacillus anthracis	Penicillin G	Erythromycin, a tetracycline. a sulfonamide.
Vibrio comma	A tetracycline + streptomycin?	A tetracycline + kanamycin?
Toxoplasma gondii	A sulfonamide + pyrimethamine	
Actinomyces israeli (bovis)	Penicillin G	A tetracycline, a sulfonamide.
Candida albicans	Localised nystatin or amphotericin B (locally applied)	Gentian violet.
Systemic fungal infections	Amphotericin B	

which will be antagonistic. The laboratory data are not always applicable to the disease processes in humans.

The bactericidal drugs more effectively attack the multiplying bacteria and hence, if a bacteriostatic drug is used along with a bactericidal agent, inhibition of bacterial multiplication may reduce the efficacy of the bactericidal agent. Combination of penicillin with chlortetracycline has been shown to produce antagonistic effect in pneumococcal meningitis. A similar antagonistic effect occurs in children treated for bacterial meningitis with the combination of ampicillin and chloramphenicol as compared to ampicillin alone. This, however, is not always true as the action of penicillin is not antagonised but enhanced by addition of sulfonamides. It is postulated, therefore, that if a bacteriostatic drug is added to the bactericidal agent two things may happen:

(1) if the organisms are highly sensitive to the bactericidal drug antagonism may occur, while

(2) if the organisms are relatively resistant to the bactericidal drug, additive effect may be seen.

Combination of bacteriostatic drugs is usually additive and there is no evidence that any such combination exerts an effect superior to that of the more active of their constituents. Combination of bactericidal drugs among themselves may cause synergistic effect particularly with the drugs with different mechanisms of action. Since little is known regarding various mechanisms of anti-bacterial action with most of the drugs, the data regarding such clinically useful combinations are limited.

Conditional resistance occurs when an organism is resistant to one of the antibiotics competing for the same ribosomal binding site. The inactive drug by preventing the ribosomal binding of the active agent could then interfere with the effective action by the other drug. Antagonism of this type occurs with combinations of the bacteriostatic agents like erythromycin, chloramphenicol and lincomycin.

Combined antibiotic therapy involves certain risks. These are:

(1) increased risk of superinfection by resistant organisms,

(2) emergence of organisms resistant to multiple drugs used,

(3) increased danger of allergic and multiple toxic reactions,

(4) sense of false security which may lead to incomplete evaluation and inadequate therapy of the patient, and

(5) increased cost of therapy.

It is recommended, therefore, that the combinations should be used only when indicated and the best known combination should be selected. Readymade combinations should not be used routinely, as they do not allow adequate doses of the major drugs and it is difficult to adjust the doses according to the patient's need. Furthermore, one should be critical about the combination recommended on the basis of laboratory evaluation or an inadequately controlled clinical trial in man.

Antimicrobial prophylaxis: Use of antibiotics in prophylaxis of certain diseases is well established. It must be remembered, however, that a drug which can cure a disease does not necessarily prevent it. Circumstances where such chemoprophylaxis may be useful are:

(1) for preventing meningococcal infection in healthy children during an epidemic; for prevention of diseases like syphilis, gonorrhea, malaria, bacillary and amebic dysentery. Syphilis in newborn can be prevented by treating the mother during pregnancy;

(2) for preventing endocarditis following minor surgical procedures like tonsillectomy or tooth removal in patients with cardiac lesions and for preventing repeated attacks of streptococcal infection particularly in patients with history of rheumatic fever;

(3) during certain surgical manipulations for preventing invasion of blood stream by pathogens e.g. catheterization in patients with urinary infection, colonic surgery, open heart surgery;

(4) in patients with compound musculoskeletal injury, penetrating wounds and skull injuries with rhinorrhea and otorrhea;

(5) to prevent microbial complications like bronchopneumonia, severe cases of measles, small pox and tetanus;

(6) in comatose or paralytic states to prevent aspiration bronchopneumonia e.g. in poisoning cases; it must be emphasised that routine use of prophylactic antibiotics in all unconscious patients is of no benefit and may cause complication;

(7) in hepatic failure, given orally for preventing the development or worsening of coma, where they are believed to act by inhibiting the intestinal organisms which produce ammonia.

The indiscriminate use of antibacterial agents in chemoprophylaxis, however, can be hazardous because such a procedure may cause adverse and allergic reactions, produce resistant organisms and cause superinfection due to other nonsusceptible pathogens. Thus, the procedure may often lead to a higher rather than a lower rate of infection.

In clean surgical operations, routine prophylaxis with antibiotics is unnecessary and not recommended, Routine prophylactic antibiotic therapy to prevent secondary infection in conditions like mild viral upper respiratory infections in children, congestive cardiac failure and in the newborn delivered after prolonged labour, is not of any benefit. As pointed out in an editorial in the Lancet "the unwarranted use of antibiotics and particularly broad-spectrum antibiotics in a mistaken prophylactic attempt is a sin and it would be wise to 'avoid not only the sin but also the occasions of sin' by better understanding of the epidemiology of gram-negative bacteria and the application of aseptic and other methods designed to prevent these bacteria colonising or infecting patients."

Antibiotics are not likely to be useful in chemoprophylaxis, if they are given to prevent colonization by various organisms in the internal and external environments of a patient. They are, however, useful when used as a single specific agent to prevent or destroy the infection due to specific organism.

Bacterial resistance: Drug resistance is not a characteristic of all bacteria and many organisms responsible for common infections have remained susceptible to antibiotics e.g. *pneumococci*, *streptococcus pyogenes* and *meningococci*. The host defense, environmental factors and the properties of the drug used, influence the development of bacterial resistance to a drug.

Bacterial resistance is often quantitative and not qualitative. Thus, an antibacterial substance which is not effective in small doses may inhibit the bacteria *in vitro* in large concentrations. This, however, is not of much clinical significance as such high levels can rarely be achieved *in vivo* owing to possible toxicity. High concentrations may sometimes be useful for treating resistant local infections.

Bacterial resistance is either natural or acquired. The development of acquired bacterial resistance can be demonstrated *in vitro* by serially culturing the organism in increasing concentrations of an antibacterial drug. Organisms thus made resistant *in vitro* usually again become susceptible to the drug following their serial subculture in the drug free medium. On the other hand, the organisms which are naturally resistant or those which develop resistance after exposure to the drug *in vivo* usually retain this property.

In organisms which are naturally resistant, the drug sensitive enzyme reaction may be absent. Some naturally resistant organisms may elaborate a substance which destroys the antibiotic e.g. *E. coli* produce penicillinase which destroys penicillin. Following the use of antimicrobial agent which destroys the sensitive strain, these naturally resistant variants multiply and become dominant; there is no change in bacteria themselves involved.

Microbes can acquire drug resistance after a change in DNA. This change may occur by alteration in the structure of chromosomal DNA (*mutation*) or more commonly, by acquisition of extrachromosomal DNA as a result of *genetic exchange*. Genetic exchange is the more important cause of clinical drug resistance because it produces epidemic resistance to multiple drugs.

The extrachromosomal genetic element responsible for transferable drug resistance is known as episome or plasmid. It can reproduce itself within the microbial cell and then can spread to other susceptible organisms, when grown together. The extrachromosomal genetic material in case of Gram -ve bacteria is known as "R" factor. R factor may carry upto 8-10 different r-determinants, each responsible for resistance to a different drug and thus is capable of transferring multiple resistance to other bacteria.

Genetic exchange from one microbe to another may occur by the process of transformation, transduction or conjugation. Transfer of resistance through free DNA (*transformation*), though demonstrated experimentally, does not seem to occur in nature. *Transduction* is a type of gene transfer in which DNA from one bacterial cell is introduced into another bacterial cell through the agency of bacteriophages. The other mechanism by which drug resistance can be transferred to other bacteria is by physical *conjugation* (mating). On acquiring the R factor the recipient microbes can become resistant to one or multiple drugs without ever having been exposed to them.

R factors are found mainly in intestinal bacteria, especially in *E. coli*, *Enterobacter aerogenes*, *K. pneumoniae*, *Salmonella*, *Shigella*, *Proteus*, and *Pseudomonas*. Since R factors can be transferred from one bacterial species to another, regardless of pathogenecity, they can be transferred from resistant *E. coli* to *Salmonella* or *Shigella* within the human bowel. Clinically, resistant Gram-negative bacteria carrying R factors present a serious problem because their resistance to multiple drugs can be spread in epidemic proportions. Widespread outbreaks of bacillary dysentery caused by multiple-drug-resistant Shigellae have been reported from Japan, Bangladesh and South America; many of these Shigella strains carried R factors. In Mexico, multiresistant *Salmonella typhi* produced the worst epidemic of typhoid fever in modern history; and chloramphenicol resistant *S. typhi* strains have been isolated from Kerala, India. Transferable drug resistance is frequent in Gram-negative bacilli causing urinary infections.

In contrast to transfer type of drug resistance, resistance after *mutation* involves chromosomal genes. Organisms undergo spontaneous mutational changes and the mutants possess the capacity to multiply even in the presence of higher concentration of the antibiotic. Chromosomal mutations affect susceptibility to only one drug. As compared to R-factor resistance, mutational drug resistance is usually of low degree and does not spread rapidly. Streptomycin is an important example where resistant mutants are produced during therapy.

Bacteria which develop resistance may have their drug sensitive reaction substituted by a drug resistant reaction; or some of these bacteria may elaborate substances which counter the drug action, e.g. the production of PABA by sulfonamide resistant staphylococci or penicillinase by penicillin resistant staphylococci. The bacterial cell membrane permeability to the drug may be altered so that intracellular accumulation of the drug is prevented, as in case of tetracyclines.

Organisms that become resistant to one drug may exhibit cross resistance to other related compounds e.g. kanamycin and neomycin, erythromycin and triacetyloleandomycin, and polymyxin B and colistin.

In practice, resistant infections may occur because the strain originally present becomes resistant following the drug therapy or the lesion may be due to already resistant bacteria present in the environment. The problem of bacterial resistance in hospitalized patients is very important.

Already, many hospital strains of *staphylococci*, certain strains of *E. coli* and *pseudomonas* have become resistant to commonly used antimicrobial agents. Tetracycline-resistant strains of group. A beta-hemolytic streptococci are also not uncommon.

The development of bacterial resistance can be reduced by using antibiotics only when necessary. The proper drug should be selected and used in adequate doses for adequate time. Drug combinations may be employed wherever they are known to delay the development of resistance. It must be remembered, however, that since the incidence of bacterial resistance parallels the number of antibiotics employed in a given subject, unnecessary use of multiple antimicrobial agents may itself contribute to the problem of bacterial resistance.

Dangers of antibiotic therapy: Antibiotics are the most useful life-saving agents in therapeutics. But, they are potentially harmful. The harmful effects are:

(a) Development of allergic and anaphylactic reactions. Hence, antibiotics such as penicillin which are very useful for systemic infections must not be used locally.

(b) Development of multiple drug resistant organisms, the infection due to which may be difficult to manage.

(c) Development of superinfection: Superinfection can be defined as the new infection that occurs during the chemotherapy of a primary infection. This may be due to:

(i) eradication of susceptible organisms in a patient with a mixed infection leaving the resistant strains to multiply.

(ii) destruction of normal nonpathogenic bacterial flora, thus creating a bacterial vacuum leading to overgrowth of resistant organisms, and

(iii) colonization of the lesion with resistant exogenous organisms from the environment.

Superinfections are manifested by new clinical symptomatology usually related to intestinal, renal and respiratory tracts or to blood stream. Infants, patients with pulmonary diseases and those with low body defence mechanisms are more prone to get superinfections. The organisms most commonly encountered are *Staphylococci, C. albicans, E. coli, Proteus* and *Pseudomonas*. Some of the superinfections can be dangerous and may even cause fatal results e.g. resistant Staphylococcal enterocolitis and systemic fungal infections.

Superinfections are usually related to the dose and duration of antibiotic therapy. Further, they occur more frequently when large doses of two antibiotics are given simultaneously.

(d) Since certain nonpathogens in the intestinal tract are known to synthesize some vitamins like folic acid and vitamin K, destruction of the normal bacterial flora may cause deficiency of these vitamins.

(e) Certain antibiotics may cross the placental barrier and may produce damage to the foetus.

(f) Use of antibiotics may give false security to both the patient and the physician and the necessity of correct diagnosis and treatment may be neglected. Similarly in case of a surgeon, asepsis may be neglected in otherwise clean surgery.

(g) All the antibiotics are capable of producing selective toxicity some of which can be more serious than the disease under treatment e.g. aplastic anemia, or kidney damage.

Misuse of antibiotics: The present total consumption of antibiotics in relation to the known incidence of infections is very much in excess, indicating that antibiotics are many times misused. This obviously would create many problems as discussed above.

As stated by M. M. Wintrobe, (Prescriber's Journal 4, 1964) antibiotics should be used with caution. "A shotgun should not be used when a rifle would be better. An exact diagnosis permits the use of a specific agent instead of a 'wide spectrum' therapeutic agent which the physician hopes will bring down the target he cannot see. A cannon should not be used to kill a mouse. The risks involved in the use of a therapeutic agent should be weighed against the seriousness of the disease to be treated and the possibility of treating the condition with another agent which is less potentially toxic should be considered. The physician must at all times be alert to the possible occurrence of an adverse reaction."

From the many antibiotics now available, one needs to know only the important representatives of each class and know them well. The various conflicting advertised claims of superiority of one antibiotic over the older established drugs used for similar purpose should be critically evaluated before accepting the change in established prescribing practice.

Once started, the drug must not be changed without valid reasons and should be continued until both clinical and bacteriological cure are achieved. This may vary from a few days to many months. Too large or too low a dosage should be avoided as it may either produce toxicity or cause bacterial resistance. If any adverse effect is observed during the therapy, the drug should be withdrawn instead of using another compound to suppress it. Thus, if vomiting is induced by an antibiotic, no attempt should be made to continue the therapy by using a centrally acting antiemetic; instead, another chemotherapeutic agent should be chosen. Lastly, antibiotics should not be used routinely in all fever cases without understanding their nature simply with the hope of giving 'quick benefits' of chemotherapy.

46 Chemotherapy of Urinary Tract Infections

Urinary tract infection is a common disorder at all ages and in both sexes. A healthy and normal urinary tract is generally resistant to infection. However, in at least 50 per cent of patients, a predisposing cause cannot be demonstrated inspite of adequate investigations. In every patient with recurrent urinary tract infection, it is absolutely essential to look for the predisposing cause, especially congenital anomalies and obstructive lesions, and to treat them if present.

Urinary tract infection may present itself in acute or chronic form.

Acute infection, localized to the urethra and bladder, causes increased frequency and urgency of micturition, dysuria and pain in the perineum. Fever, chills and leucocytosis are generally absent. Such infections are generally self limiting. If the kidneys are also involved in addition to the above symptoms, patient may also have loin pains, fever, chills and leucocytosis. In certain cases, especially those during pregnancy and puerperium, septicaemia can occur. Urine is usually loaded with pus cells and a stained film of the sediment shows bacteria.

Chronic pyelonephritis may follow inadequately treated acute infections and is especially likely to develop in patients with a definite predisposing cause. Many patients, however, may not give a history of acute urinary tract infection.

Patients with chronic infection may have few ~~urinary symptoms unless renal failure~~ has supervened when polyuria may be present. General loss of health and weight, anemia and hypertension are frequently present. It must be remembered that chronic pyelonephritis is an important cause of hypertension. The urine may show a few pus cells. *Significant bacteriuria* is demonstrable in most patients with active infection and is essential for diagnosis, which cannot be made only on the basis of pus cells in the urine.

Patients having classical symptoms related to kidney, fever and pyuria have definite bacterial invasion of the kidney. However, symptom-free patients with bacteriuria as well as those with symptoms related to the lower urinary tract may also have renal tissue involvement.

In infants and children, urinary tract infection often masquerades as fever of unknown origin, failure to thrive, unexplained vomiting or even as vague abdominal pain. Hence, the diagnosis can be easily missed unless it is constantly kept in mind. Unlike in adult, it is difficult to distinguish between cystitis and pyelonephritis in this age group and hence, all urinary tract infections at this age should be treated as if they were pyelonephritis.

Pathogenesis and bacteriology: The bacteria most commonly found in the urinary tract infections originate in the rectum or in the superficial tissues of the perineum. Bladder infection in females is often preceded by the establishment of the infecting organisms in the vaginal introitus. From here, the organisms ascend to the urethra and the bladder. The few bacteria that normally gain access to the bladder are (a) washed out by the emptying of the bladder, (b) inhibited in their growth by the low pH (5.5), the high urea content and the hyperosmolality of the urine, and (c) are destroyed by a direct antibacterial action of the bladder mucosa.

Ninety-five per cent of the urinary tract infections are due to Gram-negative bacilli *E. coli* is the commonest offender and next to it is *Proteus mirabilis*, *Klebsiella*, *Aerobacter* and *Pseudomonas aeruginosa* (*pyocyanea*) are the other pathogens. *Enterococci*, *Streptococci* and *Staphylococci* account only for 5 per cent of cases. Mixed infections are likely to be present in chronic cases, in diabetics, in those with obstructive uropathies and in those with indwelling bladder catheters. Such mixed infections are more difficult to treat than those in which *E. coli* is the only organism present.

Significance of bacteria in the urine: The normal urinary tract, except for the distal urethra, is sterile. A few bacteria may, however, be sometimes found even in properly collected urine of apparently healthy individuals. The most widely used method for identification of urinary tract infection is the quantitative (colony count) culture of bladder urine. Colony counts above 100,000 per ml. are designated as *significant bacteriuria* and are considered diagnostic of infection while those below 10,000 may be regarded as due to contamination. A few apparently healthy individuals with normal urinary tracts or those on corticosteroid therapy excrete in their urine bacteria in excess of 100,000/ml. of urine. Such individuals are said to have *asymptomatic bacteriuria*. There is a reason to believe that quite often, this may be the residue of an incompletely treated or an inapparent urinary tract infection or the forerunner of such an infection. It is, therefore, imperative to treat all such individuals as if they actually had a urinary tract infection.

Urinary tract infection is a potentially serious condition and failure to realise this may lead to development of serious chronic pyelonephritis and hypertension.

Investigations of a case of urinary tract infection:

(1) The urine obtained by midstream technique or by suprapubic bladder puncture is examined bacteriologically in every case and the organism tested for its sensitivity to various antibacterial drugs. It must, however, be remembered that the *in vitro* drug sensitivity of bacteria does not necessarily correlate with the clinical response. Further, the definition of significant bacteriuria (more than 100,000 organisms per ml. of urine) applies to urine obtained by midstream technique. Any growth at all from urine obtained by bladder puncture is pathological.

Catheterization of the bladder for collection of urine is totally unjustified as it may lead to dangerous infection.

(2) Diabetes must be ruled out in every patient.

(3) Urological investigations including renal function assessment and intravenous pyelography should be carried out in every patient with chronic or recurrent urinary tract infection. Infants and children having even a single attack of urinary infection should also be investigated in detail.

DRUG THERAPY

In acute cases, an appropriate drug may be started as soon as the urine has been collected for bacteriological examination. When the results of drug sensitivity of the pathogen grown are available, another drug may be substituted for the first one, if necessary. Although the symptoms are relieved quickly, the pyuria takes a longer time to clear. Disappearance of symptoms and of pyuria, however, does not indicate that the infection is eradicated. With sensitive organisms, an appropriate antibacterial drug is usually given for 10 to 14 days. Urine must be re-examined at one week and again at the end of 6 weeks. If it is sterile on both occasions, the infection may be considered as cured. It must be emphasized that many failures are symptom-free and adequate follow-up is very necessary. Some authorities advocate continuation of drug therapy with smaller doses as 'chronic suppressive' therapy for some months till repeated urine cultures are negative.

In chronic cases, mixed infection is more likely and concomitant renal failure may modify drug therapy. In such cases, there is no desperate hurry to start drug treatment before the case is thoroughly investigated.

Duration of treatment in chronic cases will have to be longer, sometimes with various drugs given in rotation, in order to prevent the development of bacterial resistance.

Patients with asymptomatic bacteriuria must be treated adequately in order to prevent chronic renal infection.

General principles: (1) It must be noted that the significant infection is in the tissue and not in the luminal urine alone. This means that for successful treatment, the drug must achieve adequate concentration in the tissues as well as in the urine. Drugs may be bactericidal or bacteriostatic. The former are more capable of eradicating the infection. But, drug allergy and cost (as in case of ampicillin and cephaloridine respectively), drug toxicity (as in case of kanamycin and cycloserine), or quick emergence of bacterial resistance (as in case of streptomycin and nalidixic acid) may not permit the routine use of such drugs.

(2) The drug must be used in adequate doses and for adequate periods.

(3) The growth of *E. coli* is optimum at pH 6.0 to 7.0 and is inhibited at pH below 5.5 and above 7.5. The pH of the urine must also be maintained at a level that would permit optimum antibacterial activity of the drug used and would prevent crystalluria in the case of sulfonamides. Adequate alkalinization (pH 7.5) is achieved by the administration of 2 g. (½ teaspoon) of sodium bicarbonate, sodium citrate or potassium citrate, four to five times a day. Alkalinization of urine enhances the antibacterial activity of penicillins, erythromycin, kanamycin, streptomycin and gentamicin. The pH of the urine must be maintained below 5.5 when using tetracyclines, which are unstable and lose their antibacterial activity at higher pH, and methenamine mandelate, which liberates formaldehyde only when the pH is below 5.5. This can be achieved by administration of ammonium chloride (2-6 g./day), ascorbic acid (1-2 g./day), methionine (10-20 g./day). Urinary acidifying agents, however, are unpalatable and are likely to produce dangerous metabolic acidosis. Chronic administration of acidifying agents leads to the formation of an excess of ammonia in the renal medulla; this interferes with the bacteriostatic activity of the plasma. Moreover, acidification of the urine is almost impossible in the presence of infection with urea splitting organisms. Chloramphenicol is stable over a wide range of pH and hence, the adjustment of pH is not critical.

It must be emphasised that infections due to proteus and sometimes other coliforms, *Staph. albus* and some diphtheroids, give rise to alkaline urine. This is because these organisms produce urease, an enzyme which splits urea to form ammonia. In such cases, acidifying drugs will not only be ineffective but may cause fatality due to uncompensated acidosis.

(4) As frequent emptying of the bladder helps to reduce the bacterial counts in the urine and as the growth of *E. coli* is reduced if the urine is very dilute, the fluid intake should be liberal during the use of most of the drugs.

(5) There is no satisfactory antibacterial drug to which all the strain of *E. coli*, the commonest causative organism, are invariably sensitive. Hence, the initial choice of the drug depends upon the relative cost and adverse effects of the drug.

The drugs which are usually employed in the urinary tract infections are:

(a) *Bacteriostatic* agents such as sulfonamides, tetracyclines, chloramphenicol and nitrofurantoin.

(b) *Bactericidal* agents such as ampicillin, cycloserine, kanamycin, cephaloridine, polymyxins, streptomycin, gentamicin, and sulfa-trimethoprim combination.

SULFONAMIDES: Sulfonamides are effective against most of the common urinary pathogens including *E. coli*. They produce effective urine and tissue levels.

They eradicate uncomplicated *E. coli* infections in 70-80 per cent of cases but are relatively ineffective in chronic cases, complicated cases or in the presence of mixed infections.

Although they are bacteriostatic, their use is still justified in this country as these drugs are cheap, effective orally, easily available and their long term use in the treatment of urinary tract infections has demonstrated their reasonable safety.

A short acting sulfonamide such as sulfadimidine should be administered in a dose of 2 g. initially, followed by 1 g. 6 hourly daily for 10-14 days. Urinary pH should be alkaline during such therapy and fluid intake must be liberal. This initial treatment may be followed by 1 g. daily for several months. Long acting sulfonamides may be substituted for prolonged therapy.

CO-TRIMOXAZOLE (Septran, Bactrim): The combination of sulfamethoxazole and trimethoprim (see Chapter 40) is a highly potent, bactericidal combination against urinary tract infections with *E. coli.* It is also effective against Proteus species but not against Pseudomonas. In acute urinary tract infection, it is used in the dose of 2 tablets twice a day for 10 days. In smaller doses (as low as one tablet twice a week) it has been claimed to be effective in eliminating chronic bacteriuria. As trimethoprim has been reported to be teratogenic in animals, it should not be used during pregnancy. Renal insufficiency leads to retention of trimethoprim and can alter the optimum 1 : 5 ratio of trimethoprim to sulfamethoxazole in urine. The fixed dose combination is, therefore, likely to be rendered less effective in renal insufficiency.

NITROFURANTOIN: This drug is rapidly absorbed from the gastrointestinal tract. Its urinary concentration is high but it gives poor tissue levels due to rapid protein binding. It has mainly a bacteriostatic effect against common urinary pathogens except some strains of Proteus and most strains of Pseudomonas against which it is ineffective.

The dose is 400 to 800 mg. per day (depending upon the severity of the infection) in 2-4 divided doses. Although the drug is more soluble in alkaline urine, alkalinity reduces its antibacterial activity. In fact, bactericidal effect may only be obtained in an acid medium. Bacteria develop resistance slowly and prolonged administration is well tolerated.

Nitrofurantoin is given in the full dose for 10-14 days after which smaller doses (100-200 mg. per day) can be administered for several weeks to months for 'chronic suppressive therapy'.

This drug is especially useful in infections which are resistant to other, more commonly used drugs and in patients with mixed infections or infection accompanied by obstructive uropathy.

As nitrofurantoin is mainly excreted by glomerular filtration and tubular secretion, adequate urine levels of the drug are not obtained even on prolonged therapy in patients with kidney failure. The drug, therefore, should not be used in cases of renal insufficiency (creatinine clearance 20 ml/minute or less).

Nitrofurantoin exhibits therapeutic antagonism with nalidixic acid.

METHENAMINE MANDELATE (Mandelamine): This drug is a salt of mandelic acid and methenamine, and combines the antibacterial properties of both the drugs.

It is rapidly absorbed from the gastrointestinal tract and is excreted in urine. At an acid pH of less than five, methenamine liberates formaldehyde which is actively bactericidal to most Gram-negative pathogens and *C. albicans* causing urinary tract infection. Mandelic acid is bactericidal to Gram-negative organisms at an acid pH of less than five. Additional acidifying agents have to be administered to maintain the pH at the optimum level, especially in infections with ammonia producing organisms. Even after the use of acidifying agents the pH of the urine cannot be maintained at a sufficiently low level in the presence of ammonia forming organisms such as *Proteus* and *Pseudomonas.*

The drug is available as 500 mg. and 1 g. tablets. It is used in a dose of 1 g. four times a day. The fluid intake should be restricted during treatment with this drug.

Adverse effects except gastric discomfort are rare. Bacteria do not develop resistance to it. It should not be used along with sulfamethizole as the latter drug forms an insoluble precipitate with formaldehyde.

It is not a primary drug for treatment of acute infection but is of value in chronic suppressive treatment.

NALIDIXIC ACID (Gram-O-Neg): This drug is available in 0.5 g. tablets. The dose is 4 g. per day in divided doses for 10-14 days.

It has no special advantages over the other drugs and its use is reserved for the occasional case where the organism (especially *Proteus*) shows resistance to other drugs. (See Chapter 40).

AMPICILLIN: Ampicillin is effective both orally and parenterally. It is bactericidal to *E. coli, aerobacter* and certain strains of *proteus. Pseudomonas* is resistant to it and it is ineffective against penicillinase producing strains of *Staph. aureus.* It produces good tissue levels and is excreted unchanged in the urine in high concentration. It is well tolerated.

When used in a dose of 0.5 g. six hourly for 14 days, it is capable of totally eradicating majority of urinary tract infections due to *E. coli.* Many infections with *E. coli,* especially those acquired in the hospital, are found to be resistant to ampicillin. This has reduced the usefulness of ampicillin which was once considered as the drug of first choice in urinary tract infections.

CYCLOSERINE: Cycloserine is excreted in urine in bactericidal concentrations in individuals with normal renal function. The drug is used in a dose of 0.25 g. orally twice a day and the fluid intake is restricted to 1500 ml. per day. It is highly effective in eradicating uncomplicated *E. coli* infections and its bactericidal action is independant of urinary pH. It is less effective in other types of cases. Doses in excess of 500 mg. daily may cause serious toxicity. The drug should not be used in patients with impaired renal function. (See Chapter 47).

TETRACYCLINES: Tetracyclines act on most of the common urinary tract pathogens except *Proteus* and *Pseudomonas.* They are used in a dose of 250 mg. six hourly for 10-14 days. If necessary, in certain cases the treatment is followed by prolonged suppressive treatment with either sulfonamides or nitrofurantoin, whichever is more appropriate.

Tetracyclines produce adequate tissue and urine levels. They, however, are bacteriostatic and resistant bacterial strains emerge rapidly following these agents. Tetracyclines should be avoided in renal insufficiency and during pregnancy. (See Chapter 44).

CHLORAMPHENICOL: Chloramphenicol gives good tissue levels but only 5-10 per cent of the drug reaches the kidney in the active form. Chloramphenicol is effective against *E. coli* and other common pathogens. Occasionally, *Proteus* and *Pseudomonas* are more sensitive to it than to other drugs. However, because of its potential toxicity, its use in urinary tract infections is not routinely recommended except when it is the drug of choice as indicated by bacterial sensitivity tests. As it is handled by the body by metabolic degradation in the liver, it is a relatively safe drug to employ in the presence of renal insufficiency. It is used in a dose of 0.25-0.5 g. six hourly for not more than 10-14 days. (See Chapter 44).

AMINOGLYCOSIDE ANTIBIOTICS: These drugs (Streptomycin, Kanamycin and Gentamicin) are effective against most strains of *E. coli* and *Proteus* and the last (Gentamicin) is effective against Pseudomonas as well. These drugs are not absorbed orally, are mostly excreted by glomerular filtration and are ototoxic and nephrotoxic. They must be administered carefully in renal failure. They are administered parenterally and their use is generally reserved for urinary tract infections accompanied by septicemia. Their antibacterial action is markedly enhanced by an alkaline pH of urine. Of the three, gentamicin is the least toxic and the most preferred (though the most expensive) drug. Some strains of Proteus may, however, be most sensitive to streptomycin which, then becomes the drug of choice. Streptomycin is used in the dose of 0.5 g. intramuscularly twice a day, kanamycin 0.25 g. six hourly and gentamicin 80 mg. three times a day; they are usually continued for a period of 10-14 days (Also see Chapter 42).

CEPHALOTHIN: This is a valuable drug which is effective against the penicillin resistant *staphylococci* as well as in *E. coli* or *Proteus infection* with septicemia. It is the drug of choice for klebsiella infections. It is not effective orally, and is very costly. Its antibacterial spectrum is similar to that of ampicillin.

It is given intramuscularly in a dose of 0.5 g. every 6-8 hours till the infection is controlled. (Also See Chapter 43).

CARBENICILLIN: This antibiotic has already been discussed in Chapt. 41. In the dose of 1 gm. four times a day, it is useful in *Pseudomonas pyocynea* infection of the urinary tract in which it is combined with gentamicin. They must, however, not be mixed in the same vial or syringe because carbenicillin inactivates gentamicin.

POLYMYXINS: Polymyxin B and the related drug colistin, though bactericidal, are too toxic for routine use and should be used only against *Pseudomonas* which does not respond to other drugs.

Colistin is given in the dose of one million units or more, eight hourly, intramuscularly till the infection is controlled.

METHICILLIN: This drug, as usual, is reserved for penicillin resistant staphylococcal infection. The dose is 1 g. six hourly intramuscularly for 10-14 days. (See Chapter 41).

Choice of the drug: For the first attack, which is most often due to *E. coli,* sulfonamides should be given a trial while the report of urine culture is awaited. If they fail to eradicate the infection, ampicillin, nitrofurantoin, co-trimoxazole or tetracycline should be tried. These drugs and methenamine mandelate, cephalothin or cycloserine are the drugs used in resistant or chronic cases. For 'chronic suppressive' therapy, sulfonamides, nitrofurantoin, methenamine or co-trimoxazole can be used. In septicaemic cases, the choice rests among gentamicin, kanamycin cephalothin and carbenicillin. Polymyxin and methicillin are reserved for infections with pyocyneus and resistant staphylococci. In the presence of renal failure, tetracyclines, except doxycycline, must be avoided but chloramphenicol is relatively safe. The dose of aminoglycosides must be scaled down according to the creatinine clearance (Table 45.2). Nitrofurantoin and nalidixic acid do not achieve adequate urinary concentration in patients with renal failure; moreover, the systemic toxicity of nitrofurantoin is increased in such patients. Tetracycline should be avoided in young children.

Some women seem to get a urinary tract infection following every sexual intercourse and in some of them it may produce urgent symptoms. Such a patient should be initially treated by a full course of a suitable antibacterial drug. Following this, she should be advised to apply 0.5% cetrimide cream to the periurethral area before coitus and to empty her bladder immediately after the sexual act. This may be followed by a single dose of ampicillin 250 mg or nitrofurantoin (100 mg) after each coitus.

Follow up: Patients with acute urinary tract infection should be followed up after treatment for at least 6 months and urine cultures should be repeated at 1-2 months intervals. Cases with recurrent acute infection or with chronic infection need prolonged suppressive drug therapy after the initial treatment; in these cases follow up cultures at regular intervals should be done for about two years.

It has been demonstrated that unarrested kidney infection not only leads to pyelonephritis but also prevents the kidney growth in children. Results in children with kidney infections indicate that daily sulfadimidine (0.25 gm. for less than 1 year; 0.5 gm. for 1 to 5 years and 1 gm. for more than 5 years of age) or nitrofurantoin (2-4 mg./kg.), given over a prolonged period, reduces markedly the incidence of pyelonephritis and helps to restore the kidney growth. Ampicillin is probably better and safer for this purpose.

Prophylactic antibacterial therapy: This is indicated under the following circumstances:

(1) following instrumentation of the urinary tract,

(2) when an indwelling catheter is left in the bladder,

(3) in patients with uncorrectable congenital anomalies of the urinary tract, and

(4) asymptomatic bacteriuria.

Sulfonamides, nitrofurantoin and ampicillin are the most commonly employed agents for this purpose. It must be remembered, however, that doses which are employed for long term suppressive therapy may not produce adequate tissue levels. Thus, although the urine may remain sterile a renal infection may continue to progress without being detected.

47 Chemotherapy of Tuberculosis

Tuberculosis is an infectious disease, caused by several species of mycobacteria, collectively termed the tubercle bacilli. The important human pathogens of this class are *M. tuberculosis*, and *M. bovis*. Tuberculosis is a disease as old as mankind itself. It has been described as 'King of Diseases' in the Vedas and was mentioned by Charaka and Sushruta, about 600 B.C. With the discovery of tubercle bacillus, the causative organism, by Robert Koch in 1882, the disease became known as tuberculosis.

Tuberculosis is a systemic disease, the commonest form in man being the chronic pulmonary variety. It can also involve other organs. Though the disease is usually chronic, acute fulminating forms such as tuberculous pneumonia or generalized miliary tuberculosis can also occur.

According to the World Health Organization, there are probably 15 to 20 million cases of active tuberculosis in the world today, some 2 or 3 million new cases appear and some 1-2 million die of tuberculosis every year, while an unknown number are cured' after treatment. Out of the 20 million active cases, nearly 75 per cent exist in the developing countries, mainly in Asia and Africa. In India, it is estimated that about 6 million cases of tuberculosis exist and a quarter of these are infectious. The important causative organism in India is *M. tuberculosis*.

Like other chronic infections, tuberculosis is a difficult disease to treat. The major reasons for this are:

(a) Caseation necrosis, a unique feature of tuberculosis, allows the bacilli to remain in a dormant condition by sealing off the communication of the necrotic area with the communicating channel like bronchus and ureter. When the communication opens, the solid caseous material is autolyzed and the liquid contents are expelled, resulting in the development of a cavity with a caseous lining. When the dormant bacilli get an access to the atmospheric oxygen, they multiply rapidly, producing a spread of the infection and an increase in the size of the cavity. Bronchial stenosis or ureteric constriction which may occur as sequelae, prevent adequate drainage of the caseous material.

(b) The caseation also tends to block the blood vessels supplying the necrotic area, making penetration by antitubercular drugs difficult. The caseated material itself is also impenetrable to majority of the chemotherapeutic agents.

(c) Tubercle bacilli remain viable and multiply even when ingested by macrophages. Majority of the chemotherapeutic agents (except INH, rifampicin, pyrazinamide and ethambutol) penetrate poorly into the macrophages.

(d) The organisms may develop resistance to the chemotherapeutic agents.

No effective chemotherapeutic agent was available for treating tuberculosis till as late as 1940. The treatment then mainly consisted of rest, fresh air and good food. In addition, surgical methods like phrenic nerve avulsion, artificial pneumothorax and pneumoperitoneum were widely employed. The discovery of para-aminosalicylic acid by Bernheim in 1941 was the first step in the development of effective therapeutic agents. The other two commonly used agents, streptomycin and isonicotinic acid hydrazide, were discovered in 1944 and 1952 respectively.

Drug therapy has now revolutionized the treatment of tuberculosis and forms the most important aspect of its management. The antitubercular activity of drugs can be studied *in vivo* by producing experimental tuberculosis in animals like guinea pigs, mice, rabbits and monkeys. To study the effect of drugs on tubercle bacilli inside macrophages, mononuclear cells (macrophages) are obtained from peritoneal exudates induced in guinea pigs or rabbits by intraperitoneal administration of mineral oil or glycogen. Such cells can be maintained alive *in vitro* for several days and they phagocytose virulent tubercle bacilli. The fate of the intracellular micro-organisms can be followed microscopically following exposure of the infected cells to antitubercular drugs, added to the tissue culture medium. This technic is called 'Mackaness macrophage technic'.

The chemotherapeutic agents available for treatment of tuberculosis can be divided into:

I. **Standard drugs—used in the initial treatment:** Streptomycin, Isonicotinic acid hydrazide (INH), Rifampicin, Ethambutol, Para-aminosalicylic acid (PAS) and Thiacetazone.

II. **Reserve drugs—used in resistant cases:** Pyrazinamide, Morphazinamide, Ethionamide, Capreomycin, Viomycin, Kanamycin and Cycloserine.

STANDARD CHEMOTHERAPEUTIC AGENTS

STREPTOMYCIN: This antibiotic is considered in detail in Chapter 42. Streptomycin is both tuberculostatic and tuberculocidal *in vitro*, depending upon the concentration; but *in vivo*, it mainly acts as a tuberculostatic agent. The antitubercular activity of the antibiotic is less than that of INH. It does not penetrate into the caseous foci or the macrophages and its passage into the cerebrospinal fluid is inadequate (especially when corticosteroids are used concurrently) to achieve effective therapeutic concentration within the central nervous system.

Primary resistance to streptomycin is seen in 2 to 3 per cent cases of tuberculosis. When streptomycin is used alone, permanent bacterial resistance develops in 3 to 5 months. However, when it is used in combination, the development of resistance may be delayed for a year or more.

Streptomycin should be used with caution in the elderly and in those with renal impairment. 0.75 g. daily is now considered the preferred regime in such patients.

ISONICOTINIC ACID HYDRAZIDE (INH): This is one of the most effective chemotherapeutic agents against *M. tuberculosis* both *in vivo* and *in vitro*. The drug acts mainly on organisms in an active state of division (Fig. 47.1).

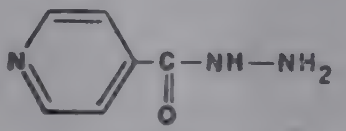


Fig. 47.1: Isonicotinic acid hydrazide

Mechanism of action: The exact mechanism of action of INH is not known. It has been suggested that the drug inhibits phospholipid synthesis and damages the cell membrane of tubercle bacilli. Intracellular or extracellular chelation of divalent cations essential for bacterial metabolism is another possible mechanism of action. Evidence has also been presented showing the ability of INH to suppress the formation of DNA and RNA, particularly the former. In addition the drug inhibits various oxidative mechanisms. It is a tuberculocidal drug and acts on both extracellular and intracellular organisms but does not affect other bacteria.

INH resistance: If it is used alone, the mycobacteria can develop resistance to INH very rapidly. The importance of *in vitro* INH resistance, however, is doubtful as it does not correlate with the drug response in patients, where the drug can still continue to remain effective. INH, therefore, should not be discontinued because of apparent failure to achieve therapeutic objectives or because of *in vitro* evidence of resistance, but the other drug administered along with INH should be changed.

Primary INH resistance, where the bacilli fail to respond to INH *in vivo* is rare. Such

INH resistant mycobacteria are non-pathogenic in guinea pigs but pathogenic in man.

Absorption, fate and excretion: INH is rapidly absorbed on oral administration. Peak plasma levels are reached within an hour and fall to about 50 per cent or less within 6 hours; effective blood levels may persist for as long as 24 hours. The absorption of the drug from the gastrointestinal tract is so complete that oral and parenteral doses produce comparable plasma and tissue levels. After absorption it is uniformly distributed throughout the body. It appears in kidney, muscle, spleen, lungs, brain, intestines and skin and penetrates into the saliva, milk, pleural and cerebrospinal fluids. The concentration of the drug in CSF in normal human volunteers is about 1/3rd of the plasma levels but in the presence of tubercular meningitis, higher (50%) concentrations are achieved. It can cross the placental barrier freely.

INH penetrates intracellularly and diffuses into macrophages and the necrotic centres, and even after the drug has disappeared from other tissues like brain and muscles, tissues like liver, skin, lungs and caseous material still retain an appreciable amount of the drug. Tuberculostatic concentrations of INH may persist for as long as 4 days in caseous masses, after a single oral dose.

INH is mainly metabolized in the liver by acetylation. Individuals may differ in their ability to metabolize the drug. Thus, *rapid inactivator* is a subject whose 6 hour serum level of biologically active INH following a single test dose of 4 mg. per kg. is 0.2 μg. per ml. or less, while *slow inactivator* is one, whose 6 hour level is 0.8 ug per ml. or more after an equivalent dose. Rapid inactivation is a genetically determined characteristic that is found commonly in Japanese and Eskimos and has also been demonstrated in Indians. It was formerly believed that the rapid inactivators would require a larger dose of INH for therapeutic effect and the slow inactivators would be more prone to develop INH toxicity. It now appears that the fast inactivators are particularly susceptible to hepatic damage because they produce more acetylhydrazine, a hepatotoxic agent. PAS competes with INH for acetylation mechanism and taking INH and PAS together results in higher plasma and urine levels of free INH than when they are taken separately. This may enhance the therapeutic efficacy of both drugs.

Approximately 75 to 95 per cent of orally administered INH is excreted in the urine within first 24 hours. The main degradation products are acetyl isoniazid and isonicotinic acid. In addition, small quantities are excreted after conjugation with glycine and as isonicotinoyl hydrazone. Of all these, only free INH has antitubercular activity. Less than 1 per cent of INH is excreted in feces in an unchanged form.

Adverse reactions: In general, INH is a remarkably safe drug. The most important toxic effects of INH encountered clinically involve the peripheral and the central nervous systems. The toxic manifestations are:

(i) **Intolerance:** This is usually manifested with symptoms of fever, malaise and skin eruptions, sometimes with lymphadenopathy and occasionally with jaundice.

Allergic reactions may involve various organs. Hepatitis, infectious mononucleosis, blood dyscrasias and diffuse vasculitis have been reported with isoniazid therapy.

(ii) **Peripheral nervous system:** The drug causes peripheral neuritis leading to anaesthesia, paraesthesiae, burning and pain along the distribution of sensory nerves in extremities. It has been found that isoniazid depletes the tissues of pyridoxine. Pyridoxine deficiency produces peripheral neuritis, sometimes accompanied by anemia and skin changes. Neuropathy is more frequent in slow inactivators than in rapid inactivators. Its incidence is also dose related. It is rare with the 200-300 mg/day regime but is more frequent with twice a week high dose regime. It also tends to be more frequent in poorly nourished patients. In the dose of 10-15 mg. per day, pyridoxine may prevent such neuropathy. Pyridoxine administered daily in the dose of 100 mg. in 2 or 4 divided portions effectively counters the peripheral neuropathy. Its routine prophylactic use along with the 200-300 mg/day regime is not recommended except in malnourished patients for fear of interference with the antituberculous action of INH. It is, however, given routinely in the dose of 10 mg. daily in patients on the high-dose twice a week regime.

(iii) **Central nervous system:** INH stimulates the CNS and may cause convulsions. Psychotic behaviour may be seen even with a normal dose but such episodes are commoner in patients with a history of epilepsy or psychosis. The psychic disturbances consist of euphoria, transient loss of memory, separation of ideas and reality, and loss of self control. Large doses of the drug may cause ataxia, muscle twitching, paraesthesiae, stupor and toxic encephalopathy. Toxic doses (40 mg. per kg. or higher) may cause severe metabolic acidosis, hyperglycemia and glycosuria, seizures and coma.

Optic neuritis leading to atrophy may rarely develop. For this reason, fundoscopic examination should be carried out periodically during therapy and treatment should be discontinued if visual disturbances develop.

(iv) **Miscellaneous:** These include dryness of mouth, urinary retention in the male and epigastric distress. INH depresses the hepatic biotransformation of diphenylhydantoin and the latter drug may prove toxic when used in combination with INH. It may also cause hepatotoxicity.

Preparations and dosage:

(i) Isoniazid tablet I.P. contains 100 mg. of the drug. Usual dose, 200 to 300 mg. (3-5 mg/kg) daily. In twice weekly regime, 14 mg/kg twice a week. In miliary and meningeal tuberculosis, 10-15 mg/kg daily. In chemoprophylaxis 5 mg/kg daily.

(ii) Isoniazid syrup containing 50 mg. of drug per ml. is available. It is administered in the dose of 5 mg. per kg. per day.

(iii) Isoniazid injection N.F. for children contains 100 mg. of isoniazid per ml.

RIFAMPICIN (Rifadin, Rimactane): It is a semisynthetic derivative of rifamycin B, isolated from *Streptomyces mediteranei*. It is highly active against *Staph. aureus* and *albus* and *Cl. welchii*. It is as effective as erythromycin or lincomycin against *Streptococcus viridans* and *beta-hemolyticus*, *Pneumococci*, *Bacillus anthracis*, *C. diphtheriae*, *N. gonorrhoeae* and meningococci. It is only moderately active against *H. influenzae* and *Streptococcus faecalis*. It is also active *in vitro* against many Gram-negative bacilli like *E. coli*, Proteus, Salmonella, Shigella, *Pseudomonas aeruginosa* and Brucella. However, unlike penicillin, many organisms develop early resistance to rifampicin. Its most important property is its effectiveness against *Mycobacterium tuberculosis*. This organism is inhibited by doses of the same magnitude as with INH. The antibiotic is effective against tubercle bacilli resistant to the standard chemotherapeutic agents and against majority of the atypical mycobacteria.

Rifampicin is believed to act by inhibiting DNA-dependent RNA polymerase, thus stopping the expression of bacterial genes. It is bactericidal and acts against both intra- and extra-cellular organisms.

Absorption, fate and excretion: Rifampicin is well absorbed from the gut. After a dose of 600-900 mg. orally, given at least ½ hour before breakfast, the peak level is achieved within 2-3 hours and therapeutically useful concentration persists for more than 12 hours.

Food and PAS interfere with its absorption and lower plasma levels are achieved when rifampicin is given either with food or with PAS. The drug is largely metabolized to desacetyl rifampicin which undergoes entero-hepatic circulation and which is as active against *M. tuberculosis* as rifampicin.

Rifampicin is excreted in the urine; about 25% of the 600 mg. dose is excreted in an active form in 24 hour urine.

Almost 85% of the drug gets bound to serum proteins. Hence, levels in CSF, pleural and ascitic fluids are about 15% of serum level. The drug crosses the placenta.

Since rifampicin is largely metabolized by the liver, the serum concentration is raised in liver diseases while renal failure has little effect.

Adverse reactions: On daily rifampicin regime, adverse reactions are uncommon. They are more frequent and more serious during intermittent rifampicin administration. They include skin rashes, diarrhoea, ataxia, dizziness, eosinophilia and leucopenia. In a few cases fatal liver damage has been reported. Patients on rifampicin therapy should be told that their urine, faeces, saliva, sputum, tears and sweat may become orange red in colour. Recently, acute hepatic and renal failure have been reported in patients taking rifampicin intermittently. Influenza like reactions with shock have also been reported with this drug. Although it causes teratogenic effects in animals, they are not reported in human beings; but at present, it is better to avoid rifampicin during pregnancy, unless there are compelling reasons to use it. Antibodies to rifampicin have been reported during large-dose intermittent therapy.

The drug may induce hepatic microsomal enzymes and thus could cause increased catabolism of hydrocortisone, oral contraceptives and digoxin.

Therapeutic uses: Because of the likelihood of the emergence of resistant bacteria and availability of other potent antibiotics for the Gram-positive and negative organisms, rifampicin is mainly reserved for the treatment of tuberculosis. Usually, a daily dose of 10 mg./kg. is recommended, given as a single dose. Rifampicin 450-600 mg. along with INH 300 mg. in a single oral dose is as effective as or even superior to combined regimen with streptomycin and INH. It should not be used in the same regime as PAS.

It could also be used with advantage for the treatment of meningococcal carriers and for serious staphylococcal septicemia, due to organisms resistant to conventional drugs. It has also been reported to be useful in the treatment of leprosy.

ETHAMBUTOL (Themibutol, Myambutol): Ethambutol is the dextrorotatory isomer of 2, 2' (ethylenediamine) -di-l-butanol. The levorotatory form is inactive against the mycobacteria but is equally toxic. It is effective against mycobacteria resistant to INH, PAS, streptomycin and ethionamide as well as against many atypical mycobacteria. Primary resistance to this drug has not been reported. When it is used along with other drugs, resistance to ethambutol develops slowly, and the development of resistance to the second drug is greatly delayed.

The mechanism of action of ethambutol is not precisely known. The drug acts mainly against rapidly multiplying organisms.

Absorption, fate and excretion: Nearly 70 per cent of the drug is absorbed after oral administration. It penetrates into erythrocytes which probably serve as the depot from which the drug is released into circulation. It, however, does not persist in other tissues and fluids, the CSF level being only 20% of the plasma level.

Approximately 50 per cent of the orally administered drug is eliminated in urine within 24 hours. About 10 per cent of the drug is metabolized and excreted in urine.

Adverse reactions: The drug produces ataxia, muscular weakness, loss of vision and laboured breathing in monkeys. In man, the drug may produce optic nerve toxicity even in small doses. The early symptoms are blurring and haziness; this is followed by progressive decrease in visual acuity, contraction of the visual fields, central scotomas and poor colour discrimination, particularly, loss of ability to see green colour. The symptoms may disappear when the drug is discontinued. Peripheral neuritis and retrobulbar neuritis have been reported. The incidence and severity of these reactions are usually dose related. The drug should be avoided in young children because of the difficulty in identifying early reduction in visual acuity in them. Other adverse reactions include anaphylactic shock, nausea, anorexia, confusion, headache and allergic reactions.

Preparations and dosage: Ethambutol is administered orally in the daily dose of 25 mg. per kg. for 8-12 weeks, after which the dose is reduced to 15 mg. per kg. per day. The drug is generally given as a single daily dose for 8-12 months. The dose in children is 20 mg. per kg. per day, given in two divided doses. Tests for visual acuity should be done before, during and after the treatment.

PARA-AMINOSALICYLIC ACID (PAS): PAS is a synthetic compound with bacteriostatic activity. It stops the growth of actively multiplying tubercle bacilli both *in vivo* and *in vitro*. However, it is far less potent than INH and streptomycin and a continuous blood level of the compound has to be maintained to achieve an adequate tuberculostatic activity. The drug, therefore, is of little value when used alone. Its main use is to act as a companion drug to a more potent drug such as INH.

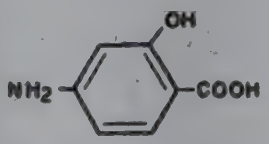


Fig. 47.2: PAS

As the anti-tubercular activity of PAS is antagonized by para-aminobenzoic acid (PABA), the drug is believed to act by interfering with the utilization of PABA by the mycobacteria. Sulfonamides also act by a similar mechanism but are not effective in tuberculosis. This may be because of the exacting receptor structure of the tubercle bacilli, which accommodates PAS or PABA but rejects sulfonamides. PAS does not affect any other micro-organisms and is devoid of analgesic and antipyretic activities.

Therapy with PAS alone results in the emergence of resistant tubercle bacilli within about 4 months.

Absorption, fate and excretion: PAS is rapidly absorbed on oral administration. Following a single dose of 4 g., peak plasma levels are reached within 1 to 2 hours and detectable plasma levels persist upto 6 hours. Approximately 50 to 60 per cent of the drug in the plasma is bound to plasma proteins. PAS is rapidly distributed throughout the body water, reaching all organs and tissues but penetration into the CSF is poor. It diffuses readily into caseous masses and accumulates in elastic fibres. Unlike INH, it does not persist in either normal or tuberculous tissues and disappears rapidly from the body when medication is stopped.

Para-aminosalicylic acid is mainly metabolized by acetylation. Nearly 85 per cent of the drug is excreted in urine within 7 hours. Small amounts are secreted in bile, milk and saliva. The free form of the drug may form calculi in the urinary tract. This danger is prevented by keeping the urine neutral or alkaline, or by using the soluble sodium salt of the drug. Renal impairment and probenecid retard the urinary elimination of the drug.

Adverse reactions: Even though serious toxic reactions with PAS are rare, the incidence of adverse effects is higher than with INH or streptomycin. The important toxic manifestations are:

(i) **Intolerance:** Allergic reactions like pruritus, skin rash, low grade fever, malaise and eosinophilia may occur. Severe anaphylactic reactions are rare. The drug may produce severe shock when given intravenously in individuals with impaired liver function.

An illness closely resembling infectious mononucleosis has been reported with PAS therapy. It is characterised by fever, malaise, headache and exanthema. The Paul Bunnel agglutination test, however, is negative.

(ii) **Gastrointestinal tract:** Gastrointestinal irritation is the commonest side effect of PAS therapy. A large percentage of patients experience anorexia, nausea, epigastric burning, abdominal distension and diarrhoea. These symptoms are severe and frequent when the drug is taken on an empty stomach. In most cases, gastrointestinal symptoms subside after reduction in the dose. The symptoms clear up rapidly on discontinuation of the drug.

There is some evidence that the drug may cause peptic ulcer and occasionally may produce haemorrhage from an existing ulcer. Hence, it should not be given in the presence of peptic ulcer.

Gastrointestinal irritation with PAS can be minimized by taking it after meals, or by taking milk or antacids just before the drug.

(iii) **Haemopoietic system:** The blood dyscrasias produced by PAS include leukopenia, megaloblastic anemia, agranulocytosis, thrombocytopenia and acute hemolytic anemia. Jaundice and hepatic damage may occur occasionally.

(iv) **Miscellaneous:** These include proteinuria and hematuria due to renal irritation. Occasionally, serious water and electrolyte depletion and acute renal failure may develop. Transient pulmonary infiltration with or without marked eosinophilia, resembling Loeffler's syndrome may rarely develop during PAS therapy. The drug may produce metabolic acidosis secondary to urinary loss of bicarbonate in persons with emphysema or a chronic respiratory disease and in children. Rarely, prolonged PAS therapy may cause goitre, sometimes with myxoedema, as the drug inhibits iodine binding and thus interferes with the synthesis of thyroxine. The drug may rarely cause hypokalemia.

Among INH, PAS and Streptomycin, PAS is the most toxic, the least effective and the most expensive compound.

Preparations and dosage:

(i) Sodium aminosalicylate tablet I.P. contains 0.5 g. of the drug. Dose: 10 to 15 g. daily, in divided doses, by mouth. The individual dose of PAS should not be less than 5 g.

(ii) The other preparations available include para-aminosalicylic acid granules N.F., sodium para-aminosalicylate granules N.F., and the potassium and calcium salts of PAS. Calcium benzamidosalicylate, the calcium salt of a PAS congener, is claimed to produce more prolonged blood levels than sodium para-aminosalicylate.

THIACETAZONE: Thiacetazone, a thiosemicarbazone derivative, initially discarded because of its toxicity, is now being used in low doses, as a cheap substitute for PAS to act as a companion drug to INH. INH-Thiacetazone combination is almost as effective as INH-PAS combination. Initial resistance to thiacetazone sometimes exists, but it is uncommon. When it is used alone, the mycobacteria rapidly develop resistance to this compound. When it is given with streptomycin, it does not significantly delay the resistance to streptomycin and is inferior to PAS in this respect. Further, it can increase streptomycin toxicity by displacing streptomycin from plasma protein binding and by interfering with its renal excretion.

The drug is satisfactorily absorbed from the gastrointestinal tract. Peak plasma levels are reached within 4 hours. It rapidly diffuses into the various body tissues and also crosses the placental barrier. About 40 per cent of the drug is excreted in urine within 48 hours. It is also secreted in milk.

Toxicity to thiacetazone usually manifests itself within first 3 months of therapy. Anorexia, nausea and vomiting are the commonest symptoms. Drug fever, skin rashes and Stevens-Johnson syndrome (erythema multiforme) appear occasionally. The serious toxic manifestations include progressive anemia, granulocytopenia and even agranulocytosis; it also causes kidney and liver damage.

The usual recommended dose of the drug is 150 mg (2 mg/kg) daily in a single dose given with INH.

Thiacetazone and INH tablet N.F. contains 50 mg. of thiacetazone and 100 mg. of isoniazid. Dose: 3 tablets daily in an adult.

Reserve Chemotherapeutic Agents

Majority of the reserve antitubercular drugs are less potent and more toxic than the standard drugs and hence, are used only in cases either resistant or intolerant to those drugs.

PYRAZINAMIDE (Pyraldina, Unipyranamide): This drug, related chemically to thiosemicarbazones and nicotinamide, is effective against *M. tuberculosis* of human type resistant to streptomycin and INH but is ineffective against the bovine and atypical forms of tubercle bacilli. Combination of INH and pyrazinamide in man is therapeutically equal or superior to INH-PAS combination. When the drug is used alone, resistance develops within 8 to 12 weeks.

The mechanism of action of pyrazinamide is not definitely known. The drug shows anti-tubercular activity *in vitro* only at an acidic pH and is effective against intracellular tubercle bacilli.

Absorption, fate and excretion: Pyrazinamide is rapidly absorbed from the gastrointestinal tract. After administration of a dose of 1.5 g. orally, peak plasma levels are reached within 1 to 3 hours and the drug can be detected in the plasma upto 15 hours. It is widely distributed in the body and *achieves a concentration in the CSF almost equal to the plasma levels*. The drug is de-aminated in the liver and the degradation products as well as the free drug are excreted in urine.

Adverse reactions: Most patients complain of a loathsome metallic taste and sulfurous eructations. Apart from arthralgia, anorexia, nausea, vomiting, malaise, mild skin rashes, exanthema, and rarely photosensitivity resulting in bright red-brown discolouration of the exposed parts of the body, the serious toxic effects involve the liver.

Toxic hepatitis may occur at any time during the course of treatment, as early as the 7th day and as late as the 8th month. It does not appear to be dose-related. Jaundice supervenes in 3 to 4 per cent of cases and deaths due to hepatic necrosis have been reported. The drug, therefore, is contraindicated in the presence of hepatic insufficiency and patients receiving it should be closely observed for the evidence of hepatic damage.

Rise in serum uric acid level due to increased tubular reabsorption of urates and precipitation of gouty arthritis have been reported in some patients after prolonged therapy with pyrazinamide.

Preparations and dosage: This drug, available as 500 mg. tablets, is administered orally in adults in the dosage of 25 mg/kg/day (not exceeding 2 g day) in one or 2 divided doses. For children, a dose of 20 to 30 mg. per kg. is given daily.

MORPHAZINAMIDE (Dynazide): This anti-tubercular drug, bearing a close structural similarity to pyrazinamide, is claimed to be more potent than the parent compound. The drug has been administered orally in the daily dose of 2 to 3 gm. along with INH, PAS or ethionamide. The side-effects are similar to those of pyrazinamide.

ETHIONAMIDE (Rigenicid, Trescatyl). Ethionamide is a drug with a chemical structure closely related to that of INH. It differs from the latter in the absence of the hydrazide side chain. Ethionamide is effective against tubercle bacilli resistant to other drugs and has proved effective in infections due to atypical mycobacteria. It is effective against intracellular as well as extracellular organisms. It is believed to act by inhibiting the protein synthesis in the cell. Resistance can develop both *in vivo* and *in vitro*. Such organisms show cross resistance to thiosemicarbazones.

Absorption, fate and excretion: Ethionamide is absorbed fairly rapidly from the gastrointestinal tract. It is a gastrointestinal irritant. After a single oral dose, peak plasma levels are reached within 1 to 3 hours and they drop to 25 per cent by 8 to 9 hours. The drug is widely and rapidly distributed in the body tissues and achieves a significant concentration in the CSF. The metabolic fate of the drug is not known. Less than 1 per cent of the drug is excreted in the active form in urine.

Adverse reactions: The toxicity of ethionamide is considerable and makes drug withdrawal mandatory in about 30 per cent of cases. Mild allergic manifestations include skin rashes and alopecia, but occasionally, serious manifestations like purpura and anaphylactic shock may develop. Gastrointestinal disturbances occur in majority of the patients and include anorexia, nausea, vomiting, diarrhoea, weight loss and a metallic taste in the mouth. To minimize gastrointestinal irritation, the drug may be given in a single dose after the evening meal or at bed time. It is also advisable to start with a small initial dose and to increase it gradually.

The nervous system disturbances are similar to those observed following INH but occur more frequently. The neurotoxicity is enhanced when the drug is combined with INH. The drug also causes toxic hepatitis.

The miscellaneous toxic effects include endocrinological disturbances like gynecomastia, menorrhagia, impotence and an increased difficulty in controlling diabetes mellitus because of hypoglycemic episodes. Pellagra-like symptoms including stomatitis and diarrhoea have been reported in a few cases.

Preparations and dosage: Ethionamide is available as 125 and 250 mg. tablets. The optimum dose of the drug is 1 g. daily; because of gastrointestinal intolerance, it is administered initially in the dose of 250 mg. twice daily and then increased gradually by 250 mg. every fortnightly. Children tolerate the drug better than adults and the recommended daily dose for them is 12 mg. per kg. given in 3 divided doses.

CAPREOMYCIN: This antibiotic is obtained from *Streptomyces carpreolus*. It is a polypeptide, highly soluble in water. Its *in vitro* activity against mycobacteria is about half that of streptomycin and it is effective against mycobacteria resistant to the standard chemotherapeutic agents. Resistance *in vivo* and *in vitro* to the antibiotic has been reported but it occurs slowly. Mycobacteria resistant to viomycin are sensitive to capreomycin but those resistant to capreomycin are no longer inhibited by viomycin. It has little activity against other bacteria.

Absorption, fate and excretion: Because of its destruction in the stomach, the antibiotic has to be administered parenterally. Following intramuscular injection, peak plasma levels are reached within 1 hour, are maintained for 2 to 3 hours and the drug is entirely eliminated from the plasma within 24 hours. Kidney damage results in high blood levels.

Adverse reactions: The adverse effects are similar to those of streptomycin including allergy, renal and eighth nerve damage. Cataracts have been observed in animals receiving capreomycin. Though this phenomenon has not been reported in man, regular eye examination during therapy with the drug is advocated. The drug also causes weakness associated with hypokalemia, hypocalcemia, and hypomagnesemia.

Capreomycin should be administered with caution in the presence of renal impairment. The antibiotic should not be combined with streptomycin, kanamycin or viomycin but may be combined with other agents like PAS, INH, cycloserine, pyrazinamide and ethambutol that are neither ototoxic nor nephrotoxic.

Preparations and dosage: The recommended dosage schedule for adults is 15 to 20 mg. per kg. (approximately 1 gm.) daily, intramuscularly, for 60 days and then twice weekly for 18 months. Suggested dosage in children is 15 mg. per kg. given according to the similar dosage schedule.

KANAMYCIN: This antibiotic has been discussed in detail in Chapter 42. The antibiotic is active against mycobacteria resistant to streptomycin, PAS, INH and cycloserine but is not effective against those resistant to viomycin.

Kanamycin has been used intramuscularly along with ethionamide or cycloserine for the treatment of resistant cases in doses similar to those of capreomycin. It should not be used with other ototoxic and nephrotoxic drugs. Children appear to be less susceptible to kanamycin ototoxicity than adults.

CYCLOSERINE (Themiserine): It is an antibiotic useful in the treatment of tuberculous as well as Gram-negative infections. Cycloserine is mainly tuberculostatic. It is effective against tubercle bacilli resistant to INH or streptomycin and against atypical mycobacteria, although its antitubercular activity is less than that of these two drugs. Cycloserine probably acts by inhibiting the synthesis of the bacterial cell wall.

Absorption, fate and excretion: Cycloserine is rapidly absorbed from the gut; peak plasma levels are reached within 4 hours and decline by 12 hours. Repeated administration leads to accumulation of the drug in the plasma. It is distributed throughout the body and achieves the same concentration in the CSF as in the plasma, particularly when the meninges are inflammed.

The exact metabolic fate of the drug is not known. Approximately 50 per cent of the orally administered antibiotic appears in the urine within 12 hours of administration and 65 per cent is excreted by the kidney within 72 hours. Renal impairment leads to high plasma concentrations and development of toxicity.

Adverse reactions: The use of cycloserine is limited by its toxicity. The neurological effects include muscular weakness, tremor, increased reflexes, ankle clonus, ataxia, slurred speech and convulsions. The psychic effects include nervousness, insomnia, anxiety, psychosis, loss of judgement, lapses of memory, confusion, delusions and hallucinations. Some patients become suspicious while others become paranoid and develop suicidal tendencies. Alcoholics, patients receiving isoniazid and persons with chronic convulsive disorders are more prone to have convulsions with cycloserine. In view of its serious neurotoxicity, the drug should be avoided in patients with a history of epilepsy or psychosis and in those with renal impairment.

Preparations and dosage: It is available as tablets containing cycloserine tartrate (0.125 gm. of the base). The recommended dose of the drug is 0.5 to 2 g. daily, administered in divided doses. A satisfactory regime is to start with 250 mg. every 12 hourly, and to add 250 mg. every ten days until the patient is receiving 1-2 g. daily in about 2 months. In children, a dose of 10-15 mg. per kg. per day is used.

VIOMYCIN: This antibiotic, obtained from *Streptomyces puniceus*, is a strongly basic substance and is available as sulfate. It is freely soluble in water. The powder is stable at room temperature for approximately 2 years but the aqueous solution deteriorates after a week. The antibiotic is effective against streptomycin and INH sensitive and resistant mycobacteria. Resistance to this antibiotic develops *in vivo* but more slowly than to streptomycin. Viomycin resistant strains are usually resistant to streptomycin.

Absorption, fate and excretion: Given orally, its absorption is erratic and hence it is administered parenterally. Following intramuscular injection, the drug is rapidly absorbed. The drug penetrates poorly into the CSF and into the pleural and peritoneal cavities. Approximately 65 to 100 per cent of an injected dose is eliminated in urine within 24 hours.

Adverse reactions: These are similar to those with streptomycin but are more frequent and involve the kidney, the eighth nerve and the body electrolytes. The electrolyte disturbances are due to urinary excretion of potassium, calcium, phosphates, chloride, and retention of nitrogen. The carbon dioxide combining power of the blood is increased. The electrolyte disturbances may cause ECG changes, muscular weakness and edema. In view of the toxicity of the drug, monthly audiograms and blood urea nitrogen level determinations are advocated.

Preparations and dosage: The recommended dose of viomycin sulfate is 2 g. twice a week by intramuscular injection. The dose should be divided into two injections of 1 g. each.

MANAGEMENT OF TUBERCULOSIS

I. **Pulmonary tuberculosis:**

All patients with proven active tuberculosis must be treated. The presence of active pulmonary tuberculosis can be suspected from clinical signs and routine laboratory investigations like the ESR; nevertheless, it should be confirmed by skiagram and repeated sputum examinations. It is important to remember that an active disease can exist even in the absence of significant symptomatology. The important objects in treating tuberculosis are:

(a) To suppress the multiplication of organisms and prevent the spread of the disease;
(b) To render the patient noninfectious by arresting the discharge of organisms, and
(c) To achieve complete healing and prevent the recurrence.

Chemotherapy is the mainstay of the treatment of tuberculosis and all other forms of treatment like diet, climate and bed rest are only of secondary importance.

Adequate therapy with appropriate drugs make absolute rest unnecessary in most patients. Activity, moderate exercise and work are not harmful in asymptomatic patients. But rest is necessary in very ill patients. The type of climate is not so important. Patients with diminished pulmonary ventilatory reserve should avoid high altitudes. There is no special diet for tuberculosis; the patient should take a well balanced and adequate diet according to his or her purse and liking.

Necessity for hospitalisation will depend upon (1) the severity and extent of the lesion, (2) the general condition of the patient, (3) the presence of complications such as pneumothorax and hemoptysis. Majority of the patients can now be treated successfully as out-patients. However, patients in communicable stage of the disease should be strictly isolated from infants for a few weeks. It is reassuring to know that adequate chemotherapy makes sputum-positive patients 'non-infectious' in 3-6 weeks.

The efficacy of anti-tuberculous drugs is now established beyond any doubt. What is most difficult is how to persuade patients to take drugs regularly for adequate periods of time. Majority of treatment failures are due to either failure to take prescribed drug therapy or infection with bacilli initially resistant to drugs.

When instituting chemotherapy, it is vital to launch a vigorous attack on the mycobacteria by using an adequate, uninterrupted and prolonged drug regimen. It is likely that a second opportunity to cure the disease may not present itself because of the development of drug resistance. Reactivation obviously indicates the failure of the drugs to sterilize the lesion in the first instance; they are even less likely to accomplish this the second time.

Selection of chemotherapeutic regime: Drugs are always administered in combinations in order: (1) to delay the development of bacterial resistance, (2) to prolong the effective therapy and (3) to achieve maximum benefit with minimum toxicity.

INH and rifampicin are the most effective antituberculous drugs available. It should be noted that rifampicin and ethambutol are no longer considered as reserve drugs but as drugs to be used in the initial treatment of tuberculosis. They have been shown to effectively replace streptomycin and PAS respectively. The high cost of rifampicin, however, will not permit its routine use in all cases in developing countries for some time to come. INH is included in all antituberculous regimes.

There are many ways of combining the standard antituberculous drugs. These combinations vary in their effectiveness and the choice of the regime depends upon (1) cost, (2) administrative facilities for giving injections, (3) co-operation of the patient, and (4) drug tolerance and patient acceptability. *In countries like India, the conditions of treatment vary from ideal to barely minimum and the optimal regime may not always be practicable.* The Tuberculosis Chemotherapy Centre at Madras has done pioneering work in developing newer drug regimens to suit different circumstances.

(i) **Intensive three-drug regimes:** It is now considered advisable to treat all cases of tuberculosis with three drugs for a minimum period of 4 weeks in small lesions and for 8-12 weeks in moderate to extensive lesions with initial high bacterial load. This is done in order to rapidly arrest the multiplication of tubercle bacilli in the lesion and to prevent the emergence of drug-resistant tubercle bacilli. Many three-drug regimes are now available. They are all about equally effective. *Cost is, however, a major factor in choosing the drug regime in developing countries.*

The recommended three-drug regimes for initial phase of treatment are:

(1) Rifampicin 450-600 mg + Ethambutol 15 mg/kg + INH 200-300 mg
(2) Rifampicin 450-600 mg + Streptomycin 0.75-1 g + INH 200-300 mg
(3) Streptomycin 0.75-1 g + PAS 10 g + INH 200-300 mg
(4) Streptomycin 0.75-1 g + Ethambutol 15 mg/kg + INH 200-300 mg

All the three drugs are given daily. When rifampicin is used, 450 mg. are given to patients below 50 kg. and 600 mg. to those above this weight. When the regime includes rifampicin, all the drugs are best given together half an hour before breakfast. Thiacetazone has often been used as a substitute for PAS in regime 3 because of cheapness but it may increase the toxicity of streptomycin.

(ii) **Two-drug regimes:** These are not as effective as the three-drug regimes and are generally used for maintenance therapy after initial treatment with a three-drug regime. Considerations of drug cost and administrative cost may, however, often force physicians to use a two-drug regime right from the beginning.

When the drug ingestion is left to the patient himself, the regime is called an 'unsupervised regime'. In this sense, the three-drug regimes mentioned above and the daily, two-drug regimes described below are all unsupervised regimes. Their effectiveness may be marred by the failure of the patient to take the drugs as advised. In contrast to this, the patient may be asked to visit the treatment centre twice a week (intermittent therapy) and administered the drugs under supervision. These regimes are called 'supervised regimes' and ensure that the patient gets the prescribed drugs in the prescribed doses. Moreover, they reduce the drug-cost and are likely to reduce drug toxicity (except in the case of rifampicin, where intermittent therapy is associated with higher incidence of toxicity than daily therapy). The supervised regimes may be used from the inception of the treatment for the entire duration of chemotherapy, though this is not ideal.

The recommended, **'unsupervised,' daily**, two-drug regimes are:

(1) INH 200-300 mg + Rifampicin 450-600 mg
(2) INH 200-300 mg + Ethambutol 15 mg/kg
(3) INH 200-300 mg + Streptomycin 0.75-1 g
(4) INH 200-300 mg + PAS 10 g
(5) INH 200-300 mg + Thiacetazone 150 mg

Regimes 4 and 5 are as effective as each other but are less effective than the other three regimes. Regime 1 is the most expensive and regime 5 the cheapest among them. *Streptomycin + PAS and streptomycin + thiacetazone regimes are now not recommended.* INH and PAS should be dispensed in a combined preparation to prevent the patient from taking INH only.

The recommended, **'supervised', twice-weekly** two-drug regimes are:

(1) Streptomycin 0.75-1 g + INH 14 mg/kg
(2) INH 14 mg/kg + PAS 10 g
(3) Ethambutol 90 mg/kg + INH 14 mg/kg

In these regimes, the entire quantities of both drugs must be administered to the patient in the physician's or attendant's presence. Pyridoxine (10 mg/day) is given daily with these high dose INH regimes to prevent INH toxicity. Streptomycin + INH twice-weekly regime is the most effective among these three regimes. Intermittent, rifampicin-containing regimes cannot be recommended because of increased toxicity compared to daily rifampicin administration.

(iii) **Single drug regime:** INH has recently been used in the dose of 400 mg. once a day as the sole therapy in the treatment of non-cavitary pulmonary tuberculosis. The results are distinctly inferior to those of two drugs regimen which are, therefore, preferred. The incidence of neuropathy is high with this high dose of INH but it can be prevented by the daily administration of 10-15 mg. of pyridoxine.

As a rule, reserve drugs are rarely required in the initial treatment. They may, however, be needed because of primary resistance to the basic drugs, or because of intolerance or toxicity. When using reserve drugs, care should be taken to avoid drug combinations with similar toxic effects such as deafness or liver or kidney damage.

The response of the patient to chemotherapy can be gauged by:

(1) *The clinical improvement* as shown by a gain in weight and a feeling of well-being associated with reduction in cough and fever.

(2) *The bacteriological improvement*: Negative sputum cultures are obtained within 6 months in 90 per cent of the patients treated adequately.

(3) *The radiological improvement:* With adequate chemotherapy, cavity closure or its disappearance without surgical intervention has been reported in 75 to 90 per cent of patients.

(4) *Periodic determination of ESR.* Ideally, *in vitro* susceptibility tests to determine the sensitivity of the organisms to chemotherapeutic agents should be carried out before and during the drug therapy. This, however, is many times impracticable.

Duration of treatment: In general, in patients with pulmonary tuberculosis who have a satisfactory response with cavity closure and bacteriological quiescence, chemotherapy should be continued for a period of 12-18 months after the cavity closure. Patients in whom the disease is bacteriologically quiescent but the cavity remains present at the end of one year, need drug therapy for a total period of 2 to 3 years. The response to chemotherapeutic agents depends mainly on the duration of the lesion rather than the extent of the lesion. Lesions of recent origin, even though extensive, may be completely reversible.

Adjuvant therapy: If the tuberculosis is very extensive or is complicated by marked pulmonary insufficiency secondary to emphysema, chronic bronchitis or pulmonary fibrosis, oxygen or ventilatory assistance or both may be required. Institution of proper bronchial cleansing to evacuate bronchopulmonary secretions, and a tracheostomy if necessary, may be life-saving. Patients should avoid smoking and other respiratory irritants. Secondary respiratory infection, if present, must be promptly treated with appropriate antibiotics; so also the associated other diseases like diabetes mellitus.

Dry, hacking, spasmodic cough can be controlled by using codeine phosphate 15 mg. 3-4 times daily.

Pulmonary haemorrhage leading to hemoptysis needs prompt evacuation of the bloody bronchopulmonary secretions from the tracheobronchial tree to prevent aspiration and bronchial spread of the disease. The bleeding lung should be kept in a dependent position to avoid such a spread. The commonly used positions are the semi-reclining or the lateral. Light sedation is advisable but over-suppression of the cough reflex by morphine favours bronchial spread of the disease and atelectasis. Heavy sedation, therefore, should be avoided. If bleeding continues beyond 24 hours, bleeding time, clotting time and prothrombin time should be determined and blood transfusion should be administered.

Failure to obtain reversal of infectiousness (sputum or tracheobronchial secretions free of tubercle bacilli after smear and culture) after 3 months of therapy, or closure of cavities after 4 or 6 months demands change in chemotherapy. Failure of initial chemotherapy is likely to be due to:

(1) failure of the patient to take drugs, (2) primary drug resistance, (3) inadequate drug combinations, (4) interruption of treatment because of adverse reactions, and (5) persistent organisms which have become dormant and have, therefore, not been affected by the drugs.

All primary failure cases need drug-susceptibility studies to the standard drugs used in the treatment. Until the results of susceptibility tests are available, the patient should be put on a 3-4 drugs regime consisting of antimicrobial agents which the patient has never received before. The addition of one drug at a time to an ineffective regime must be avoided as resistance to that drug is bound to develop. If the susceptibility tests reveal resistance to all the standard drugs, INH may still be continued in combination with drugs used for interim chemotherapy.

Treatment of relapse: The treatment is initiated with three standard drugs as the bacterial resistance to one of the drugs is most likely. The chemotherapy is continued for at least a year or preferably longer after the sputum has become negative. Many reserve drugs are less effective and more toxic. Although most of the drug toxicity with these agents takes place in the early months of therapy, the hepatic toxicity of pyrazinamide and the psychoses caused by cycloserine may occur at any time during the course of treatment. Cases for retreatment with these drugs, therefore, should be hospitalized.

Organisms rapidly develop resistance to the reserve drugs. Persistent cavitation in the presence of persistently or intermittently positive sputum after 6 months of secondary chemotherapy, therefore, calls for surgical intervention.

II. **Other forms of tuberculosis:**

Severe forms of tuberculosis like tuberculous meningitis, tuberculous pneumonia, tuberculous pericarditis and acute miliary tuberculosis need intensive chemotherapy with the three standard drugs. Corticosteroids are required to overcome the severe toxemia.

Tuberculous meningitis: INH, streptomycin, rifampicin and pyrazinamide is the preferred combination in this disease. INH is used in the dose of 10-15 mg/kg/day. Some clinicians still use intrathecal streptomycin (100 mg. in adults, 25 mg. in children) or INH (25-50 mg. in adults, 10-20 mg. in children) in addition to the above regime, especially in seriously ill patients. Intensive chemotherapy is administered for 3-6 months or till CSF returns to normal. Total duration of chemotherapy should be 2-3 years. Pyridoxine supplement is given to all patients to prevent INH toxicity.

Steroids should be used in all severely ill patients, in those with a suggestion of cerebrospinal block and probably also in children under 1 year of age. The initial adult dose of prednisolone is 80 mg. per day (1 mg. per kg. in children) in 4 equally divided doses. The dose should then be gradually reduced till a maintenance level of 25 to 30 mg. daily is reached within 2 to 3 weeks. Corticosteroid therapy should be entirely stopped over 5 to 6 weeks.

The same regime including steroids is also applicable to tuberculous pericarditis and tuberculous pneumonia.

Acute miliary tuberculosis: Here again, intensive chemotherapy and corticosteroids is indicated.

Tuberculous lymphadenitis: This condition usually responds unsatisfactorily to chemotherapy which should be continued for 15 to 18 months. If no progress is apparent within 6 to 8 weeks, the glands may be removed surgically. Sometimes surgical evacuation of pus deep to the fascia is necessary.

Tuberculosis of the genitourinary tract, bones, joints, skin, larynx and intestines responds well to routine chemotherapy. For ocular tuberculosis, topical and systemic corticosteroid therapy may be required in addition to standard systemic chemotherapy. Approximately 30 per cent of patients who have tuberculous pleural effusion, develop chronic pulmonary tuberculosis within 5 years. Chemotherapy reduces the incidence of subsequent pulmonary and extrapulmonary tuberculosis in such cases. Treatment is continued for a total period of 18 months.

Adrenal corticosteroids in tuberculosis: ACTH and glucocorticoids are known to impair host defense mechanism and promote dissemination of infection. However, their anti-inflammatory action may sometimes be helpful. They have been shown to be useful in certain circumstances when the excessive inflammatory reaction of the body is likely to threaten life or is likely to lead to extensive fibrosis on healing. *They must never be used without cover of effective antitubercular chemotherapy.* The indications for the use of steroids in tuberculosis are:

1. To relieve toxic symptoms in fulminating, rapidly progressive pulmonary tuberculosis, tuberculous pneumonia or miliary tuberculosis. As they do not affect the final outcome of the treatment, they should not be used in the average case of pulmonary tuberculosis.

2. They are useful in preventing bronchial stenosis in endobronchial tuberculosis.

3. In tuberculous meningitis to reduce toxemia, to hasten the absorption of the exudate and to prevent the formation of adhesions, arachnoiditis and hydrocephalus.

4. In tuberculosis of the serous membrane, like tuberculous pleural effusion and pericarditis to hasten the reabsorption of fluid. Use of corticosteroids in abdominal tuberculosis, however, is dangerous as it may lead to intestinal perforation.

5. As an adrenal cortical replacement, e.g. in Addison's disease, when it occurs with tuberculosis elsewhere in the body.

6. To counter the hypersensitivity reactions to antituberculous drugs, particularly when the patient's condition is serious, the drugs are still effective and equally effective substitutes are not available.

7. To arrest the dire consequences in rapidly enlarging mediastinal tuberculous lymph nodes.

8. In ocular and genito-urinary tuberculosis, to prevent the serious consequences of fibrosis.

The detailed pharmacology of steroids is discussed elsewhere.

Treatment of tuberculosis is essentially a medical one, although occasionally surgical intervention is indicated. It must be emphasized, however, that surgical removal of the lesion does not mean that the disease is completely eradicated and the patient must be treated with adequate chemotherapy before, during and after such procedures.

CHEMOPROPHYLAXIS OF TUBERCULOSIS

Chemoprophylaxis of tuberculosis means the use of anti-tuberculous drugs for the prevention rather than the treatment of tuberculosis. INH is the ideal drug for this purpose as it is cheap, effective orally and has minimum toxic effects. Chemoprophylaxis can be:

(a) **Primary:** In which anti-tuberculous drugs are given to tuberculin negative uninfected persons, usually infants, who are at a great risk of exposure to tuberculous infection. INH is given in doses of 5 mg. per kg. daily usually for 3 months and at the end of this period, if the child is tuberculin negative, it receives BCG vaccine to provide active immunity. BCG vaccination should not be carried out during INH prophylaxis. If, however, INH-resistant BCG vaccine is available, it may be given together with INH.

(b) **Secondary chemoprophylaxis:** In this case, INH is given with the intention of preventing the development of a disease after infection has already taken place and the tuberculin test has already become positive. For this purpose, INH is administered in the dose of 5 mg. per kg. for a period of 1 year. This is particularly important in tuberculin positive children under the age of 5 years in whom the disease and its complications can be severe. Secondary chemoprophylaxis is also justified (a) in individuals showing tuberculin conversion from negative to positive, and (b) during corticosteroid administration and times of stress such as pregnancy, puerperium, surgery and serious intercurrent illness, in ex-tuberculous patients who have completed their anti-tuberculous treatment less than 18-24 months earlier.

B.C.G. VACCINE: *Bacille Calmette Guerin* is a strain of bovine tubercle bacillus with greatly attenuated virulence, developed in France by Calmette and Guerin. The aim of the vaccination is to increase the patient's resistance by producing an artificial primary tuberculous infection by an organism which causes only a local lesion and some swelling of the adjacent lymph nodes.

Before vaccination, a tuberculin test is carried out where 0.0001 mg. or 5 test units of purified protein derivative (PPD) obtained from the mycobacterium is injected intradermally on the ventral surface of the forearm. If the test is negative, it is repeated again after 6 weeks. If the tuberculin test at the end of 6 weeks also remains negative, then 0.1 ml. of the vaccine is injected intradermally in the deltoid region. This leads to the formation of a papule followed by an ulcer within 4 to 6 weeks. The regional glands are slightly enlarged. Healing occurs gradually thereafter, but the papule may be detectable upto a period of 12 months. After vaccination, the tuberculin test becomes positive within a period of 6 to 12 weeks indicating the development of immunity against tuberculosis.

A rare complication of BCG vaccination is a glandular cold abscess. This should be treated with INH and streptomycin in the usual way. Just an enlargement of lymph nodes needs no treatment.

Still rarer is the occurrence of fatal disseminated tuberculosis mainly in children with hypogammaglobulinemia. Those with hypogammaglobulinemia or eczema should not be vaccinated.

BCG vaccination has been conclusively shown to be useful in tuberculin negative school children, in contacts of cases with active tuberculosis and in persons living in areas with high incidence of tuberculosis. Ideally, it is given within first six months of life. Pretesting with PPD is not needed if BCG is given immediately after birth. Preliminary tuberculin testing can also be dispensed with during mass vaccination programme as administration of BCG to tuberculin positive children is not hazardous, although the reaction may be accelerated.

BCG has definitely contributed to the control of tuberculosis. From the safety point of view it is probably the safest of any vaccine in use today. WHO now recommends the use of simultaneous live vaccines (BCG + smallpox) for general use in developing countries.

BCG and host defence: Recently, BCG has received considerable attention for its property of enhancing the host defence mechanisms. BCG has been observed to stimulate the reticulo-endothelial system and confer resistance upon mice to bacterial or viral infection. Further, its administration can prevent the growth or cause regression of transplanted tumours in animals. In man, local intra-lesional injections of BCG or PPD have been observed to produce beneficial effects in skin neoplasms such as malignant melanoma, carcinoma and reticulum cell sarcoma. The effect of repeated, intravenous doses of BCG on various malignant growths such as carcinoma of the lung is now being studied. The mechanism of antimalignancy action of BCG is not well understood. It probably has immunological basis though other possibilities are not ruled out.

48 Chemotherapy of Leprosy

Leprosy is a disease caused by *Mycobacterium leprae* which cause characteristic lesions in the skin and the peripheral nerves. The disease is common in India, Burma and other tropical and subtropical countries. Although the leprosy bacillus was discovered by Hansen in 1873, almost 12 years before the discovery of tubercle bacillus, the progress in the chemotherapy of leprosy has been much slower than in that of tuberculosis. This is because, until recently, it was not possible to culture the leprosy bacillus. Although many acid fast bacilli from leprosy patients had been cultured *in vitro*, those were never shown conclusively to be leprosy bacilli. Further, unlike tuberculosis, human leprosy cannot be transmitted to animals so easily. Even in humans, prolonged intimate contact for some years is believed to be necessary before leprosy lesions can occur. From the therapeutic point of view, leprosy is one of the most obstinate diseases and needs prolonged drug therapy.

Human leprosy bacillus from nasal washings and skin biopsies has been cultivated successfully in the foot pads of mice; the sciatic nerve on the affected side has been shown to get involved. Recently, leprosy has been successfully transmitted to some species of armadillo. The infected armadillo tissues contain a large number of leprosy bacilli, thus, providing a better experimental model of human leprosy.

Types of leprosy: Clinically, there are four main types of leprosy: lepromatous, tuberculoid, indeterminate and dimorphic (borderline).

In *lepromatous leprosy*, the host resistance is low, the lesions abound in lepra bacilli and the disease progresses rapidly. The disease affects mainly the face, nose, ears, eyes and lymph glands. The typical lesion of lepromatous leprosy is a macule, a hairless, hypopigmented, circular, erythematous patch not associated with itching or anaesthesia. Macules are usually small, smooth and symmetrically distributed. Eventually, the skin becomes furrowed and nodulated, giving a peculiar 'leonine facies'. Eyelashes fall off. Later, ulceration occurs with marked tissue destruction involving eyes, nose and larynx. The nerves are affected late in the disease. Inspite of marked destruction, leprosy, *per se*, is rarely the cause of death. Histologically, the lesion of lepromatous leprosy is essentially a granuloma consisting of many macrophages, called lepra cells, containing numerous bacilli.

In *tuberculoid leprosy*, the host resistance is high, the organisms are few, nerves are predominantly affected first, and the progress of the disease is slow. The typical tuberculoid lesion is a large, flat, atrophic, hypopigmented skin area, with red, raised margin showing marked impairment of sensation. The peripheral nerves are thickened. The prognosis is better than in lepromatous leprosy and gross mutilation occurs only secondary to nerve destruction and anaesthesia. Histologically, the lesion consists of focal masses of epitheloid cells and giant cells with lymphocytic infiltration. Since this picture resembles that seen in tuberculosis, it is called tuberculoid leprosy.

The *indeterminate* or the confusing form is an early stage where the lesions are slight and do not give a clue about the type of disease.

Dimorphous leprosy is an unstable condition, where resistance is low and which becomes lepromatous if left untreated.

The diagnosis of leprosy is essentially

clinical, supported by bacteriological evidence from smears, from the lesions, nodules, earlobes or scrapings of the nasal mucosa. The lepromin test is of no diagnostic value because persons who have never been in contact with leprosy but are Mantoux positive may have a positive lepromin test. It is always negative in lepromatous leprosy and weakly to strongly positive in tuberculoid leprosy.

Although a few indeterminate and tuberculoid lesions can undergo spontaneous resolution even without treatment, all patients with active leprosy should be treated. It is, however, unjustifiable and even dangerous to treat this disease on mere suspicion. This not only exposes the patient to prolonged therapy with potentially toxic drugs but can also cause severe psychological trauma. In case of doubtful diagnosis, it is better to wait for definite signs to develop because the progress of the disease is so slow that very little harm can be done by waiting. The important aims of therapy are to achieve clinical and bacteriological cure and to treat physical deformities resulting from nerve and tissue damage. The psychological aspect of the patient and his environment also need attention.

DRUGS USED IN LEPROSY

SULFONES: Sulfones are derivatives of 4-4′ diaminodiphenyl sulfone (DDS, Dapsone) (Fig. 48.1). It is interesting to note that DDS was first synthesized in 1908 but its antibacterial property remained unknown until 1937 and its value as an important antileprotic drug was discovered only in 1941.

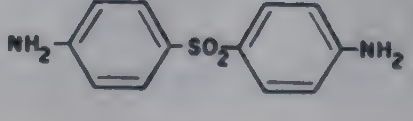


Fig. 48.1: Diamino-diphenylsulfone (DDS)

Sulfones are chemically related to sulfonamides and although they are highly effective in experimental streptococcal infection, they are too toxic for use for this purpose in man. They are, however, very useful in the treatment of leprosy.

Although many sulfone derivatives have been synthesized, dapsone still remains the drug of choice in leprosy. It has been suggested that most of the derivatives of DDS (except promacetin) act by releasing DDS in the body.

Pharmacological actions: Sulfones are specific in the treatment of leprosy. They are bacteriostatic. The mechanism of action is probably similar to that of sulfonamides and the action of DDS is antagonized by para-amino-benzoic acid.

Sulfones also exert bacteriostatic action against bacteria susceptible to sulfonamides and against the tubercle bacilli. They are, however, not used in the treatment of infection with these organisms because of their toxicity.

Absorption, fate and excretion: Absorption of sulfones varies according to the compound used. DDS is slowly but completely absorbed from the gastrointestinal tract. Other drugs like sulfetrone and promacetin are incompletely absorbed when given orally.

The peak plasma level is reached within 1-3 hours after oral administration and the drug remains detectable in the plasma for 8-12 days. Sulfones are cumulative drugs. They are distributed throughout the body fluids and tissues and can be detected in the tissues upto 3 weeks after stoppage of therapy. Sulfones get concentrated more in the leprosy-affected skin than in the normal skin. These compounds are excreted in urine as glucuronic acid conjugates and the rate of excretion varies with the type of compound. They are also excreted in large quantities in bile; this portion however, is reabsorbed. Excretion can also occur in human milk.

Adverse reactions: Sulfones are potentially toxic drugs. They commonly cause anorexia, nausea and vomiting. They can give rise to allergic reactions like dermatitis and drug fever. Skin sensitization can occur in about 3 per cent of dark skinned patients.

Fatal exfoliative dermatitis associated with drug fever, hepatitis and psychosis can rarely occur.

Sulfones are powerful oxidant drugs and can cause hemolytic anemia. Patients with G6-PD deficiency are more susceptible to their hemolytic action. They can also cause anemia, methemoglobinemia and blood dyscrasias like agranulocytosis. Other toxic effects include hematuria, liver damage and goitrogenesis.

Although the list of toxicity is formidable, with proper precautions sulfones are remarkably well tolerated by most of the leprosy patients.

Preparations and dosage:

(i) Dapsone (DDS) I.P.: 100 mg. tablets. Some authorities recommend following schedule for an adult weighing 60 kg:

Weeks 1-2 : 25 mg. once a week
Weeks 3-4 : 25 mg. twice a week
Weeks 5-6 : 50 mg. twice a week
Weeks 7-8 : 100 mg. twice a week
Thereafter : 100 mg. thrice a week

However, the possibility of producing a resistant strain does remain.

Hence, many authorities advise higher dosage starting with 25 mg. twice a week, increasing gradually to 300 mg. twice a week, or 100 mg. daily for 6 days in a week, in about 4-6 months time. With higher dosages, it is necessary to introduce regular rest periods after every 3-6 months of therapy to prevent and treat the possible adverse effects due to the drug; mild degree of anemia is common. It should be noted that extensive studies with DDS in infected mice have shown that *Myco. leprae* is highly sensitive to DDS, being inhibited by <0.01 μg./ml. of serum. The serum concentration obtained in man receiving standard 100 mg/day DDS dose is about 1.5 μg/ml. On weight basis, the dose of dapsone is 6-10 mg./kg. body wt. per week.

(ii) Dapsone injection N.F. is a 20 per cent w/v suspension of dapsone in arachis oil. Dose: 0.2 ml. intramuscularly, weekly, gradually increased to a maximum of 0.8 ml. weekly. It is useful in patients who cannot be relied upon to take oral dapsone regularly.

(iii) Sulfetrone sodium: The oral preparation of sulfetrone sodium is no more advocated. It is usually given as 50 per cent aqueous solution by intramuscular injection in doses of 0.5 ml. (0.25 gm. of sulfetrone) weekly, increasing gradually to 3 ml. weekly.

(iv) Repository sulfone, 4-4′-diacetyldiaminodiphenyl sulfone (DADDS), given I.M. in the single dose of 225 mg., gives effective blood levels of DDS for 70 to 80 days. The drug is under evaluation.

Other sulfone derivatives like glucosulfone sodium (promin), sulfoxone sodium (diasone), thiazol sulfone (promizole) and promacetin are also used but offer no advantage over the well established drug DDS.

DIAMINO — DIPHENYLTHIOUREA (Thiambutosine, Ciba 1906): It is a disubstituted congener of thiosemicarbazide. It is considered to be the best second line drug in the treatment of leprosy. It has similar activity as sulfones but it is less effective than DDS.

It is usually administered orally but can also be given by injection. Given by mouth, it is incompletely absorbed and rapidly excreted and hence it is administered daily in divided doses: 0.25 g. daily for the first month, 0.5 g. daily for the second month, 1 g. daily for the third month and 2 g. daily thereafter.

Intramuscularly, it is given as 20 per cent suspension in arachis oil. The dose is 1 ml. (200 mg. of the drug) once a week, gradually increased to 5 ml. weekly. The maximum dose advocated is 10 ml. fortnightly.

Unlike with dapsone, bacteria rapidly develop resistance to this drug. Hence, it is advocated for first 1½ to 2 years of therapy, followed by dapsone. It is mainly useful in those patients who cannot tolerate dapsone.

Adverse reactions: In recommended

doses, the drug seems to be well tolerated and serious adverse effects are not common. It causes anorexia, nausea and vomiting. Other effects include allergic reactions, dermatitis, anemia, blood dyscrasias like agranulocytosis and liver damage.

CLOFAZIMINE (Lamprene, Hansepran): This is a phenazine dye which is excreted in the urine slowly for several weeks. It is principally retained in tissues of the reticuloendothelial system. It also possesses anti-inflammatory properties. It imparts a reddish black hue to the skin of patients, which persists for several months. In the dose of 100 mg. three times a day, it is of great value in lepra reactions because of its simultaneous bacteriostatic and anti-inflammatory actions. It can effectively relieve the agonizing pain in lepra reactions in tuberculoid leprosy. It is also claimed that the drug enhances the ability of human macrophages to kill listeria.

RIFAMPICIN: This antibiotic has been discussed in Chapter 47. It is mycobactericidal and is used orally in the dosage of 600 mg. daily. Given for 2-3 weeks, it is claimed to render the patient non-contagious. The drug is less toxic than DDS and is usually given along with DDS in standard doses. The drug seems to have obvious advantages but is expensive at present.

DIETHYL DITHIOLISOPHTHALATE (Ditophal): Ethyl mercaptan compounds like dimercaprol (BAL) have been shown to inhibit the growth of acid fast bacilli. Ditophal is an ethylthiol ester which releases ethyl mercaptan *in vivo.*

It is administered by inunction in the form of cream which releases ethylmercaptan after absorption through the skin. The drug possesses unpleasant smell and is partly excreted in the breath which carries this smell. The organisms develop resistance within 4-5 months and hence, it is always given along with DDS. No serious toxic effects except allergic reaction have been reported.

CHAULMOOGRA AND HYDNOCARPUS OILS: These oils have been in use for centuries, particularly in countries like India, Burma, Thailand and Malaya. They are obtained from seeds of certain trees belonging to the genus Hydnocarpus. Chemically, both oils are almost identical with unsaturated fatty acids, chaulmoogric acid and hydnocarpic acid, as active ingredients. They were generally used by inunction over the lesion or by local intradermal injection. Following the introduction of sulfones they are no more recommended.

Other drugs which have been tried in the treatment of leprosy are:

(1) antitubercular compounds like streptomycin, INH, cycloserine, and PAS.

(2) long acting sulfonamides.

Experience with most of these compounds except perhaps long acting sulfonamides is disappointing. Sulformethoxine, a long acting sulfonamide given in the dose of 1 gm. weekly may be useful in patients who cannot tolerate dapsone.

MANAGEMENT OF LEPROSY

Leprosy, which was considered to be an incurable disease only 30 years ago, can now be successfully treated. As in the case of tuberculosis, the main difficulty in the treatment of leprosy is in persuading the patient to continue the drug therapy regularly for a prolonged period and to attend the follow-up clinic. In countries like India, adequate facilities are still not available for detecting, treating and following such cases in various villages. The medical treatment of leprosy can be wholly undertaken by practitioners or trained medical auxiliaries in the great majority of patients. Some knowledge about the natural history of the disease, details about the sulfone therapy and a sympathetic outlook towards the patient are all that is necessary for managing the leprosy patients.

Majority of the patients can be treated as outdoor patients, in mobile clinics or in primary health centres. Only a few may need hospitalization. Segregation must not be advocated very loosely as this would cause social disruption and considerable psychological trauma, particularly in a society with prejudices and traditions where a patient may be outcast for the whole of his life and made miserable. Usually, the patients developing reactions during drug therapy and those with impending eye or nerve damage need hospitalization. There is no danger in admitting any form of leprosy patient to general hospital ward, if simple principles of barrier nursing are observed and routine hygienic precautions are strictly followed.

Drug of choice and duration of therapy: Dapsone is the drug of choice in all cases of leprosy. It is highly effective, relatively non-toxic and the cheapest drug available. Resistance to dapsone develops very slowly and rarely.

The duration of therapy will depend upon the type of leprosy under consideration. In tuberculoid leprosy the drug therapy is continued for one year after all clinical signs of activity have disappeared. Clinical activity is denoted by (i) increase in size of previous lesions or the appearance of new ones, (ii) persistence of erythema or infiltration in the lesions, (iii) progressive sensory impairment and motor loss and (iv) continuation or worsening of local tenderness of peripheral nerves. The approximate total duration of therapy in tuberculoid leprosy is 2-3 years. In case of lepromatous leprosy, the treatment has to be more prolonged. It is usually continued for 2 years after all clinical and bacteriological evidence of activity has disappeared. In case of lepromatous leprosy, continued presence of hypopigmented macules or nodules indicates activity; the tenderness on peripheral nerves may also persist. Further, the persistence of acid fast debris in the smears indicates the necessity of further treatment. The total period of treatment in lepromatous leprosy is about 4-5 years. A similar schedule is advocated for dimorphic leprosy which runs an unpredictable and variable course of severity.

Following drug therapy, early lesions disappear completely. Late cutaneous lesions in lepromatous leprosy show atrophy, tissue-paper like wrinkling and scarring. In tuberculoid leprosy, nerves already damaged may remain permanently thickened. Local treatment may be necessary for neuropathic ulcerations of the extremities, caused by repeated trauma to insensitive tissues as these may not improve following systemic therapy.

Prognosis with early drug therapy is excellent and recovery is almost complete without any residual damage. Mild anemia is not a contraindication to dapsone therapy and the low dose schedule advocated is safe even in patients with hemoglobin levels as low as 60 per cent. It is not advisable, however, to treat a patient with hemoglobin less than 50 per cent. Regular hemograms are necessary in those who are receiving the drug therapy and, if necessary, the drug should be stopped and anemia corrected.

Patients who show sensitivity to DDS can be desensitized. Initially, aqueous solution of sulphetrone (Solapsone), 0.5 g. dissolved in 200 ml. water, is given by mouth twice weekly, starting with 5 ml., increasing gradually till 250 mg. of sulphetrone is well tolerated. Once this is established, 25 mg. of dapsone is substituted and then increased gradually. The drug should, however, be withdrawn completely if the rash recurs and desensitization with lower doses resumed.

In severe cases, particularly of lepromatous leprosy, full dose of dapsone may be combined with clofazimine 100 mg. daily or 3 times a week for 4-6 months followed by dapsone alone. Alternatively, rifampicin 600 mg. daily may be added to dapsone for initial 3-4 weeks with advantage. Patients not responding to sulfones within 3-6 months (probably due to drug resistance) should be treated with rifampicin 600 mg. and clofazimine 100 mg. daily for 2-3 months, followed by clofazimine alone; these two drugs are, however expensive at present.

Lepra reactions: The acute exacerbation that occurs during the course of leprosy is called lepra reaction. The pathogenesis of such reactions is unknown, but they are usually precipitated by malaria, acute infections, anxiety and following vigorous treatment with sulfones.

Lepra reactions are of two types. In one case, the existing lesions show increased erythema and swelling; the constitutional symptoms are not marked and often it leads to a decrease in the number of bacilli in the lesions. This type of reaction usually occurs in tuberculoid leprosy. Such a reaction occurring during the drug therapy may lead to complete healing of lesions. Usually, stoppage of treatment is not necessary.

The other type of lepra reaction occurs usually in lepromatous leprosy and is characterised by **erythema nodosum leprosum** (ENL). Suddenly, many crops of bright erythematous nodules and raised patches appear and the existing lesions become worse. These may be associated with fever, nerve pains, orchitis and lymphadenitis. This is a more severe reaction than the first one and the lesions may actually spread. The lepra reactions respond well to clofazimine in the dose of 100 mg. three times a day. Alternative therapy consists of chloroquine 150 mg. (base) thrice daily for two weeks or, if there is no response, injection stibophen 2 ml. intramuscularly on alternate days for six doses. Corticosteroids (prednisolone 20 to 30 mg. daily) should be used only in patients not responding to above therapy especially because of the likelihood of exacerbation of lepra reaction after stopping the corticosteroids. The severe pains of lepra reaction in tuberculoid leprosy, arising from swollen nerves constricted by the epineurium, respond well to clofazimine, failing which local intraneural injections of hyaluronidase (1500 units) dissolved in 1 ml. of 2% procaine solution and mixed with 25 mg. of hydrocortisone bring significant relief.

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After a lepra reaction, dapsone should not be started for at least two weeks after all signs of the reaction subside. When started, it should be given in a very small dose, initially under the cover of prednisolone and then increased very gradually.

Recently, thalidomide in the doses of 400 mg. daily has been reported to be highly effective in ENL. It causes constipation, diarrhoea, and dryness of mouth and is absolutely contraindicated during pregnancy. It is not much useful in other type of reaction.

Following adequate therapy, the tuberculoid or indeterminate leprosy rarely recurs and usually no treatment is necessary after the clinical cure. In case of lepromatous leprosy, the treatment has to be more prolonged. Some authorities advise continuation of DDS at half the therapeutic dose for 5-10 years after the clinical cure. In any case, patients should be followed up at regular intervals for detecting a possible recurrence.

Leprosy prophylaxis: It is advisable to avoid skin to skin contact with patients with lepromatous leprosy with open lesions. Pus from ulcers is highly infectious. Airborne droplet infection is a distinct possibility and mechanical transmission by biting insects can not be ruled out.

Antitubercular vaccine BCG has been tried with some success in the prophylaxis of leprosy. Similarly, prophylactic dapsone at half the therapeutic dose, is sometimes recommended in close contacts, particularly in children of leprotic mothers.

49 Chemotherapy of Sexually Transmitted Diseases (STD)

Sexually transmitted diseases (S.T.D.) comprise a group of infections most commonly transmitted by sexual contact; accidental infection through fomites and infection of laboratory workers are rare modes of transmission. In the case of syphilis, transplacental transmission to the foetus can occur.

However desirable, total prevention of S.T.D. is an impossible goal. Recent survey by W.H.O. indicates a worldwide rise in the incidence of S.T.D. Permissiveness, homosexuality and changing sexual practices, particularly among the adolescents, are responsible for such increase in all societies, rich and poor. Hence, chemotherapy will continue to play an important role in their treatment as in the past.

The important S.T.D. are syphilis, gonorrhea, non-gonococcal urethritis, chancroid, lymphogranuloma venereum and granuloma inguinale. The treatment of trichomonas vaginalis infection is described in Chapter 52.

Prevention of S.T.D.: Avoidance of promiscuous sexual contact is the best method of preventing S.T.D. Failing this, physical methods such as the use of a condom and thorough washing of the genitals and the surrounding areas with soap and water after an intercourse would help to prevent infection in many cases. Chemoprophylaxis of S.T.D. is controversial and is discussed below.

DRUG THERAPY OF SYPHILIS

Syphilis is caused by the spirochete *Treponema pallidum*. Penicillin is the drug of choice in the therapy of all stages of syphilis. With adequate treatment of early cases, cure is possible in over 90 per cent of cases. Arsenicals, mercurials and bismuth salts are no longer used. Penicillin resistant *T. pallidum* is so far unknown.

Before discussing the treatment in detail it is necessary to describe the various stages of the syphilitic infection:

Early syphilis is the disease during the first 4 years after its acquisition. It is divided into 'infectious' and 'latent' types and 'early neurosyphilis' (meningomyelitis).

Infectious stage is that in which the patient has the highly contagious surface lesions e.g. primary sore and the secondary mucocutaneous lesions.

Latent syphilis is that which is diagnosed only by a positive serological test in a patient who gives a history of contact but in whom no lesions are demonstrated anywhere in the body. This means that the patient has no infectious lesion and has a normal CSF. Further, there is no evidence of CNS or cardiovascular involvement.

Late syphilis is the disease after the first 4 years. It includes late latent syphilis, late neurosyphilis (GPI, tabes dorsalis), cardiovascular syphilis and gummatous syphilis involving various organs in the body.

There are several reasons for distinguishing between 'early' and 'late' disease:

(a) In the first four years, latent disease can undergo repeated infectious relapses with fresh appearance of contagious mucocutaneous lesions in spite of treatment. In 'late' syphilis, no such relapses occur.

(b) Herxheimer reaction is less severe in 'early' syphilis whereas it may lead to serious consequences in 'late' syphilis.

(c) Larger doses of penicillin and more prolonged treatment are necessary in 'late' than in 'early' syphilis.

(d) A complete cure is possible in 'early' syphilis, while it is doubtful in 'late' disease.

(e) Reversal of positive serology to negative one is possible in 'early' syphilis; it does not occur in 'late' disease. Persistence of a positive serology is, however, not an indication for more treatment with drugs.

(f) As infectious relapses do not occur in late syphilis, marriage is permitted at this stage unless the patient has crippling cardiovascular or neurological syphilitic involvement.

Principles of treatment: The spirochete is extremely sensitive to penicillin, plasma concentrations as low as 0.03 unit per ml. being spirocheticidal. This concentration must be continuously maintained for about 10 days in cases with early syphilis and about 14-20 days in cases with late syphilis. The antibiotic is always administered parenterally because oral administration of penicillin has two dangers: patients may not take the tablets regularly as advised and they may try to save some tablets for self administered chemoprophylaxis in future.

(1) Before starting treatment, the diagnosis must be established with certainty. Dark-field microscopy of material obtained from surface lesions is a must in the case of primary chancre and the mucocutaneous lesions of the secondary stage of syphilis. When surface lesions are absent, one has to rely on serological tests such as the Kahn test, Price's precipitation test, Wassermann reaction and on a more specific treponema antibody test such as the Reiter Protein Complement fixation test (RPCFT). A cerebrospinal fluid examination must be carried when neurological involvement is suspected.

(2) Treated cases should be followed up for adequate period.

(3) It is necessary to trace and treat contacts.

Treatment of early syphilis: Penicillin is administered intramuscularly by any one of the following regimes:

(1) Procaine penicillin 600,000 units daily for ten days. Such injections are relatively painless and give spirocheticidal blood levels for 24 hours.

(2) PAM 600,000 units on alternate days for 12 days. PAM is thick, has to be withdrawn and injected with a large bore needle; this is a disadvantage. To take care of the defaulters who may not complete the course, an initial dose of 2.4 mega units of PAM may be given.

(3) Benzathine penicillin, 2.4 mega units, may be injected in a single dose which gives low but effective blood levels for 2 weeks. This regimen also takes care of any possible defaulters but is likely to be painful. Also, some patients may distrust such a regime consisting of a single injection while others may take the disease lightly knowing that it can be cured by a single injection. In addition, some workers feel that it does not give adequate blood levels for the treatment of 'early' syphilis, though they recommend it in 'late' syphilis. It seems advisable to reserve this regime for patients who are not likely to co-operate for prolonged therapy.

All treated patients must be examined clinically and a quantitative serological test carried out at monthly intervals for three months, at three monthly intervals for one year, at six monthly intervals during the second year and at yearly intervals till the completion of four years from the beginning of the disease. The CSF must be examined at the end of the first year to rule out neurological involvement. During the period of observation, if there is an infectious relapse or a rise in the titre of the serological test, the penicillin course should be repeated.

Treatment of late syphilis: Late syphilis can be treated with penicillin in the same daily doses as early syphilis but the duration of treatment should be extended to about 20 days. These patients should then be followed clinically, serologically and by CSF examination (in case of neurosyphilis) at frequent intervals. Persistently positive serology is not an indication for more treatment. If, however, the test becomes positive in a higher titre, or if CSF abnormalities persist over months, treatment should be repeated. As benzathine penicillin penetrates poorly into the CSF, it should not be used to treat neurosyphilis.

Pregnancy and syphilis: Congenital syphilis is a completely preventable disease. Hence, syphilis detected during pregnancy should be treated with any of the regimes of penicillin described above. Once a patient has received an adequate course of penicillin, she need not receive penicillin treatment during each subsequent pregnancy.

Congenital syphilis detected in infants and children can be treated by injecting procaine penicillin in the dose of 100,000 units daily for 10 days. Interstitial keratitis, a common complication of congenital syphilis, needs additional treatment with local or systemic corticosteroids.

Reactions and contraindications to penicillin treatment:

(1) **Allergy** to penicillin is the only known contraindication to penicillin in syphilotherapy. It is discussed in detail in Chapter 41.

(2) **Jarisch-Herxheimer reaction:** This consists of an initial exacerbation of lesions at any stage of syphilis following the first therapeutic dose of a quick acting spirocheticidal drug like penicillin. Any reaction that occurs after second or subsequent injections of penicillin is unlikely to be due to Herxheimer phenomenon. This phenomenon is believed to be due to a rapid destruction of a large number of spirochetes probably liberating some chemical agent aggravating the local inflammatory lesion. It occurs in 90% of cases of early syphilis, and leads to an aggravation of the mucocutaneous lesions and a mild systemic illness consisting of malaise, tachycardia and fever. Lymph nodes are enlarged and tender. It lasts for 2-6 hours and is harmless. The patient should, however, be forewarned about it as, otherwise, he might feel that wrong treatment was administered. Further, the treatment with penicillin must be continued despite the reaction. In cardiovascular and neurosyphilis, however, a Herxheimer reaction may precipitate severe angina or congestive cardiac failure and psychosis, convulsions, coma or optic atrophy respectively. Fatalities have been reported following laryngeal edema or coronary occlusion.

Herxheimer reaction is an 'all or none' phenomenon and cannot be prevented by starting treatment with small doses of penicillin. The first spirocheticidal dose is likely to precipitate it. The treatment of a severe reaction is symptomatic. A glucocorticoid like prednisolone is given in doses of 30-40 mg. daily. It has also been used for preventing the reaction in patients with cardiovascular and late neurosyphilis. Its usefulness, however, is controversial. It is advisable to hospitalize the patient with late syphilis and use prophylactic sedation before starting penicillin therapy.

Other drugs: Other drugs such as tetracyclines are far inferior to penicillin in the treatment of syphilis and are used only in patients who are known to be hypersensitive to penicillin. In such patients, tetracycline or erythromycin are given orally in the dose of 0.5 g. six hourly for 15 days. Newer penicillins offer no advantage over penicillin G.

Other measures: In early syphilis, hardly any other treatment than penicillin is ever required. Marriage is usually prohibited until four years have elapsed from the acquisition of the disease. In cardiovascular syphilis, treatment of congestive cardiac failure and surgical treatment of aortic lesion, if feasible, may be required in addition. In patients with general paralysis of insane (GPI), fever therapy is sometimes helpful. Fever is usually produced by injecting the malarial parasites (*P. vivax*) which produce fever upto 105°F lasting for 4-6 hours. Such 10-12 bouts are allowed to occur and then controlled by an anti-malarial drug. How fever therapy helps is not known.

DRUG THERAPY OF GONORRHEA

Gonorrhea is caused by *gonococci*, most strains of which are sensitive to penicillin.

A few strains are, however, known to be penicillin resistant. Eradication of acute, uncomplicated gonococcal infection caused by penicillin sensitive organism is easy. When a local complication such as a periurethral abscess or prostatitis or a more distal complication such as salpingitis, parametritis or epididymo-orchitis is present, or in case of penicillin resistant organisms, eradication of the infection is difficult. Gonococcal infection is more difficult to diagnose and treat in females than in males.

Before starting chemotherapy, the diagnosis must be established by smear and culture of material obtained from the urethra and prostatic massage in the males and the urethra, vagina, cervix or Bartholin's glands in the females. A quantitative gonococcal complement fixation test on patient's serum should be done at the beginning as it serves as a guide to patient's progress after treatment.

Penicillin is the drug of choice in majority of the cases and should be tried first unless the patient is known to be allergic to it or is found to have infection with penicillin resistant gonococci. In the latter instances, tetracycline should be used.

Acute uncomplicated cases: The treatment of choice is 4.8 mega units of penicillin G in aqueous solution, divided into two doses and injected at different sites at one visit; 1 g of probenecid is given at least 30 minutes before the injection of penicillin G. The procedure is repeated in case of failure of the patient to respond. An alternative is to give 3.5 g of ampicillin in a single oral dose, together with 1 g of probenecid. The other alternative is an injection of procaine penicillin 1.2 mega units along with 1 mega unit of crystalline penicillin, followed by two similar injections at 24 hour intervals. Other drugs which have been found to be effective are, kanamycin 2 g. or cephaloridine 2 g. intramuscularly, both given as a single dose. Tetracycline, if indicated, should be used in the dose of 0.5 g. every six hours for 3 days. Cotrimoxazole (2 tablets twice a day for 5 days or 4 tablets twice a day for 2 days) has also given good results. Further, it does not mask syphilis. The response to treatment is usually prompt and dramatic. The patient should be advised abstinence from alcohol for about 2 weeks and sexual abstinence till he is declared as cured.

Complicated cases: Either procaine penicillin (2 mega units daily for 8-10 days) or tetracycline (0.5 g. every six hours for 7-10 days) may be used. Additional treatment consists of such measures as surgery, local irrigations with antiseptic lotions, local heat and prostatic massage. In resistant cases, aqueous penicillin G is administered daily for 5 days in the same manner as in acute uncomplicated cases. In patients allergic to penicillin, tetracycline can be used in the dose of 1.5 g. (single dose) followed by 0.5 g. four times a day for 4 days. Other drugs such as cotrimoxazole, spectinomycin, cephaloridine and kanamycin have also been used.

Treated patients should be followed up clinically, bacteriologically and serologically at frequent intervals for at least six months before they are declared as 'cured'. It must be remembered that, 'cure' is not synonymous with 'relief of symptoms'. The course of the antibiotic may have to be repeated if symptoms persist or recur or if the serum antibody titre rises during the follow up. If symptoms persist in spite of adequate treatment, the patient should be investigated for associated *trichomonas vaginalis* infection.

All patients treated for gonorrhea should be investigated regularly and frequently for the development of positive serological test for syphilis. This, however, is less practicable with the uneducated population where initial therapy with penicillin may mask the early manifestation of concomitant syphilitic infection. In such circumstances, either penicillin should be used in full doses for 10 days or gonorrhea should be treated with kanamycin sulphate (2 g. I.M.) or cotrimoxazole which does not mask syphilis.

Chemoprophylaxis of S.T.D.: Chemoprophylaxis of syphilis is not generally favoured for several reasons:

(1) Chemoprophylaxis is not 100 per cent effective. It may only mask the early clinical manifestations.

(2) Infectious relapses can occur even in treated cases for as long as four years and hence, patients need follow up. Chemoprophylaxis is likely to produce a false sense of security and discourage the patient from attending such follow ups. In addition, the risk of CNS involvement (early neurosyphilis) is higher in haphazardly or incompletely treated cases.

(3) If the patient remains without external manifestation of early syphilis, he may never know that he has contracted the disease and may then get serious late complications such as cardiovascular or late neurosyphilis.

(4) Chemoprophylaxis may encourage further promiscuity in some patients while worrying about its efficacy may lead to neurosis in others.

With the drugs available, chemoprophylaxis of gonorrhoea is probably more successful than that of syphilis.

If a person who has had sexual contact consults a doctor in less than 24 hours and requests chemoprophylaxis, an injection of 2.4 g. of procaine penicillin can be given to prevent gonorrhoea and syphilis. Alternative regimes for prevention of gonorrhoea are: kanamycin 2 g. intramuscularly; ampicillin 2 g. (single oral dose) together with 1 g. of oral probenecid; or demethylchlortetracycline given in two doses of 1.2 g. each at 4 hour interval. *Even in these circumstances, the patient should be kept under observation for at least three months for the development of syphilis.* In case more than 24 hours have elapsed since the sexual contact, a drug which would not mask syphilis may be used to prevent gonorrhoea. The patient should then be kept under close observation for the development of syphilis for at least three months and the disease treated fully should it develop.

A pregnant woman who has been exposed to a suspicious sexual contact or a member of the hospital personnel who accidentally exposes himself or herself to the risk of getting infected during the conduct of his or her duties should immediately be given a complete course of penicillin and then followed up adequately as if he or she had actually developed the infection.

DRUG THERAPY OF NON-GONOCOCCAL URETHRITIS

Non-gonococcal urethritis may be due to:

(a) infection with *trichomonas vaginalis* (See Chapter 52).

(b) a generalized urinary tract infection or

(c) **Nonspecific urethritis:** This common S.T.D. is now believed to be caused by *chlamydia trachomatis* in about 50% of the cases. The cause in the remaining cases is obscure. The patients complain of dysuria and a variable amount of urethral discharge; the disease shows a tendency to frequent recurrences. The diagnosis is by exclusion of gonococcal and trichomonal infections in cases of urethritis. The drug of choice is tetracycline 500 mg six hourly for 2 weeks. The sexual partner of the patient should be treated at the same time to prevent a re-infection of the patient. During therapy, the patient should abstain from sexual intercourse and alcohol (which aggravates urethritis in some men). An alternative is to give doxycycline 200 mg initially, followed by 100 mg every 24 hours for 2 weeks.

DRUG THERAPY OF CHANCROID

Chancroid or soft sore is caused by *Ducrey's bacillus.* The diagnosis is made by clinical findings and a specific skin test.

The organism is not susceptible to penicillin. A sulfonamide (e.g. sulfadimidine) given orally in the dose of 1 g. six hourly for 6 days is effective before suppuration has occurred in the regional (inguinal) lymph nodes. Once suppuration has occurred, streptomycin should be injected in the dose of 1 g. twice a day for 5 days. Tetracyclines are also effective but are likely to mask concomitant syphilitic infection and hence, should be avoided. Sulfonamides and streptomycin do not mask syphilis.

DRUG THERAPY OF LYMPHOGRANULOMA VENEREUM

This disease is caused by chlamydia. Tetracycline 0.5 g. six hourly for 2 weeks is effective in curing the acute inguinal disease; acute rectal disease requires 3 weeks of therapy. In the chronic hypertrophic type, surgery may be needed in addition to tetracyclines, for 6-8 weeks. The prognosis in chronic cases is poor. Sulfonamides are claimed to be as effective as tetracyclines.

DRUG THERAPY OF GRANULOMA INGUINALE

Granuloma inguinale is caused by *Donovania granulomatis*. The infection responds well to tetracycline which is administered in the dose of 0.5 g. six hourly for 14 days. Ampicillin in the dose of 250 mg. six hourly for 3-11 weeks is also effective. Streptomycin and chloramphenicol are less useful.

DRUG THERAPY OF VENEREAL WARTS

This condition is due to a local virus infection without any systemic effects and is sexually transmitted in 60% of cases. The warts grow rapidly in the presence of moisture and are inhibited by dryness. They are treated either by electric cautery under local anaesthesia or by applying podophyllin resin (20% suspension in liquid paraffin or alcohol). The surrounding skin must be protected from podophyllin by application of soft paraffin.

50 Chemotherapy of Malaria

Malaria is caused by parasitic protozoa of the genus *Plasmodium* and is characterised by fever with rigor, anemia and splenomegaly. The disease is still a major public health problem in many of the developing countries of Asia and Africa. The annual death rate from malaria still exceeds 1 million. The advent of powerful chemotherapeutic agents coupled with extensive eradication measures against mosquitoes has considerably reduced the incidence of this disease in India. However, due to the development of resistance by the vectors to the conventional insecticides, reversal of the results started early and by 1976 nearly seven million parasite positive cases were detected in India.

Life cycle of plasmodium: There are four major types of plasmodia which infect man, namely *P. vivax, P. falciparum, P. ovale* and *P. malariae.* P. vivax causes benign tertian malaria which, though mild, has a tendency to relapse. P. falciparum infection results in malignant tertian malaria, a fulminating infection, which, if not promptly treated, may result in death; but the disease, once cured by the drugs, has no tendency to relapse. In both P. vivax and P. falciparum infections, the infected individual develops pyrexia with rigors every 3rd day, and hence the term 'tertian'. P. ovale and P. malariae infections are not so common and are usually mild; the infected individual develops pyrexia every 4th day and hence, it is described as 'benign quartan'.

An individual is infected by malarial parasites through the bite of a female Anopheles mosquito. The disease can also be transmitted by transfusion of infected blood and from mother to foetus by the passage of organisms across the placenta. The salivary glands of the infected female Anopheles mosquito contain a large number of *sporozoites* and these are introduced into the blood stream of the host, namely man, during the course of mosquito bite. These sporozoites disappear rapidly from the circulation and invade the parenchymatous cells of the liver, and cells of the reticuloendothelial system, where they grow and sporulate. This is known as the *pre-erythrocytic stage* of the infection. The duration of the pre-erythrocytic stage varies with the species of plasmodium. It is 5 to 7 days for P. falciparum and 8 days to several months for P. vivax. The host does not develop any symptoms during this phase. At the completion of the pre-erythrocytic phase, the infected reticuloendothelial cell, termed schizont (primary exoerythrocyte form) ruptures and releases several thousand *merozoites* into the blood stream. These invade the erythrocytes and undergo further development and multiplication, giving rise to erythrocytic schizonts (asexual erythrocyte forms). The young parasites in the erythrocytes are known as *trophozoites.* These eventually rupture, causing the release of thousands of merozoites into the blood stream. This periodic release of merozoites from the infected erythrocytes is associated with a paroxysm of fever with rigor. The merozoites, released into the blood stream, invade fresh erythrocytes, again undergoing erythrocytic schizogony. A proportion of merozoites re-enter the liver and other reticuloendothelial organs and undergo schizogony. This process, termed *exoerythrocytic stage,* perpetuates infection and produces relapses even when the erythrocytic schizogony has been completely suppressed. In P. falciparum infection, exoerythrocytic stage is absent.

Some of the released merozoites may undergo differentiation into male (*micro-*

gametocyte) and female (*macrogametocyte*) sexual forms. During a mosquito bite, these forms are sucked in from the peripheral blood and undergo further development into gametes in the body of the mosquito. The female gamete is eventually fertilized by the motile male gamete resulting in the formation of a zygote. The zygote invades the gut wall of the mosquito to form an ookinete which matures into an oocyst. The mature oocyst contains several thousands of sporozoites. After about 1 to 4 weeks, depending upon the species of plasmodium, the oocyst ruptures, releasing free sporozoites into the body cavity of the mosquito. Sporozoites eventually reach the salivary glands of the mosquito.

In the life cycle of plasmodium, the female Anopheles mosquito not only serves the purpose of propagating infection but is also essential for the development of certain stages of the parasite. It is, therefore, called a *vector*.

Clinically, the malarial infection can be controlled by drugs used in the following ways:

I. **True causal prophylactics:** These are the drugs that would destroy the sporozoites before their invasion of the host reticuloendothelial cells. No drug of this type, however, is available.

II. **Causal prophylactics:** These drugs prevent the maturation of or destroy the sporozoites within the infected hepatic cells and thus prevent erythrocytic invasion. They are also known as primary tissue schizonticides. Primaquine, pyrimethamine and proguanil act as causal prophylactics against *P. falciparum* but their efficacy against *P. vivax* is doubtful.

III. **Suppressives:** These drugs inhibit erythrocytic schizogony and thereby prevent the rupture of the infected erythrocytes. This leads to freedom from rigors and pyrexia. They may not necessarily eradicate the infection. The various suppressive agents include quinine, 4-amino-quinolines, mepacrine, proguanil and pyrimethamine. Treatment with suppressives can cure *P. falciparum* infection as the parasite does not undergo exoerythrocytic schizogony. Since these drugs do not affect the persistent tissue phase of *P. vivax*, relapses can occur with the stoppage of suppressive therapy.

IV. **Radical curatives:** This term refers to eradication of both erythrocytic and exoerythrocytic schizogony so that relapse does not occur. Radical cure of falciparum malaria can be achieved with suppressives alone. For radical cure of vivax infection, only the 8-aminoquinolines are effective and of these, primaquine is the only agent used in therapeutics, usually along with suppressives like chloroquine.

V. **Gametocidal drugs:** Majority of the antimalarial agents are effective against gametocytes of *P. vivax*, but have little action against those of *P. falciparum*. Primaquine is, however, highly effective against gametocytes of both species. Proguanil and pyrimethamine do not destroy gametocytes but prevent their development in the mosquito.

Antimalarial drugs can also be classified according to their chemical structure as follows:

I. Cinchona alkaloids: Quinine.
II. 4-aminoquinolines: Chloroquine, Hydroxychloroquine, Amodiaquine.
III. 8-aminoquinolines: Primaquine, Pentaquine, Pamaquine.
IV. Acridines: Mepacrine.
V. Biguanides: Proguanil, Chlorproguanil, Cycloguanil pamoate.
VI. Diaminopyrimidines: Pyrimethamine.
VII. Miscellaneous: Sulfonamides, Sulfones.

CINCHONA ALKALOID

QUININE is an alkaloid isolated from the bark of the cinchona tree, originally a native of South America, and known for many years as 'Jesuit's bark'. Quinine is the oldest of all the therapeutic agents used in the treatment of malaria. With the advent of safer drugs, quinine is now relegated to a minor position in antimalarial chemotherapy; nevertheless, it is still a useful agent in the treatment of cerebral malaria. Interest in this drug has been reawakened with its efficacy against chloroquine-resistant P. falciparum infection encountered in Vietnam.

Pharmacological actions:

(a) **Antimalarial action:** Quinine is schizonticidal and, therefore, useful only as a suppressive. It has no effect on sporozoites and the persistent tissue forms. Resistance to quinine *in vivo* has not been reported.

(b) **Other actions:** Quinine has been termed as 'general protoplasmic poison'. It depresses a variety of enzymatic processes, reduces ciliary activity and inhibits phagocytosis and the growth of fibroblasts. It also possesses local anaesthetic activity. It has quinidine-like action on the heart; thus, it directly depresses the myocardium, reduces its excitability and conductivity and lengthens the refractory period. Intravenous quinine can produce profound hypotension due to depression of the myocardium and dilatation of the arterioles. In concentrations slightly above those required to produce local anaesthesia, quinine causes edema, pain and reactive fibrosis. Because of its irritant action, oral administration of quinine often results in nausea, vomiting and epigastric pain while excruciating local pain, sterile injection abscesses and venous thrombosis may occur after its intramuscular and intravenous use respectively.

Quinine has an intensely bitter taste and was used formerly to stimulate appetite. Quinine has a mild analgesic and anti-pyretic activity. It stimulates the uterine smooth muscle, particularly during pregnancy and has a curarimimetic action on the skeletal muscles.

Absorption, fate and excretion: Quinine, administered orally, is almost completely absorbed from the small intestine; peak plasma levels are reached within 1 to 3 hours after a single therapeutic dose. Approximately 7 per cent of the drug is bound to plasma proteins. It penetrates poorly into the CSF but readily crosses the placental barrier.

Quinine is mainly metabolised in the liver and the degradation products eliminated in urine. The plasma half life of quinine is about 10 hours but is usually prolonged in falciparum infection because of liver impairment. Approximately 5 per cent of the total administered dose is excreted in urine unchanged. A decrease in the urinary pH facilitates the excretion of the free form by minimising its tubular reabsorption. Urinary excretion is complete within 24 hours and cumulation does not occur under ordinary conditions.

Adverse reactions: The major reason for the decline in popularity of quinine is its toxicity. Poisoning is usually due to clinical overdosage or to idiosyncrasy. The fatal adult dose of the drug is estimated to be approximately 8 g. The salient toxic manifestations are:

(a) **Cinchonism:** This syndrome, which occurs when quinine is administered in full doses for a long time, resembles salicylism. When mild, the symptoms consist of ringing in the ears, nausea, headache and visual impairment. With large doses, tinnitus, deafness, vertigo, blurred vision, disturbances of colour vision and photophobia appear. Toxic amblyopia occasionally leading to total blindness has been reported. The retina becomes pale and the arteries are contracted. With severe intoxication, skin rashes, headache, fever, vomiting, confusion and delirium are seen. As the poisoning progresses, the skin becomes cold and cyanotic, the respiration is depressed, blood pressure falls, coma ensues and eventually death occurs due to respiratory arrest. Even if the patient recovers, visual and auditory impairment are not entirely corrected.

The treatment of quinine poisoning is essentially symptomatic.

(b) **Idiosyncrasy:** The idiosyncratic manifestations are similar to those seen with cinchonism but occur with a therapeutic dose of the drug. The commonest manifestation is intense flushing accompanied by generalized pruritus. Quinine may precipitate angioneurotic edema or asthmatic attacks in sensitive individuals. Rarely, quinine can cause thrombocytopenic purpura, hemolytic anemia and agranulocytosis.

(c) **Black water fever:** This condition, characterised by acute hemolysis, hemoglobinuria and fever and sometimes progressing to acute renal failure, is encountered with chronic *P. falciparum* malaria. Focal hepatic necrosis may develop in severe cases. Black water fever may occur during the natural course of malaria, and less frequently following quinine treatment. Carefully matched blood transfusions may be life saving. Once anuria sets in, the management is that of acute renal failure including hemodialysis. Usefulness of adrenocorticosteroids is doubtful.

(d) **Miscellaneous:** This includes cardiac toxicity like ventricular arrhythmias. Acute renal damage leading to anuria and uremia occurs infrequently. Intravenous administration of quinine may cause convulsions, probably due to circulatory depression and this may be followed by coma and fatal respiratory failure. Quinine may very rarely cause abortion.

Preparations and dosage: Quinine is a white powder with an intensely bitter taste, almost insoluble in water.

(i) Quinine bisulfate tablet I. P. contains 300 mg. of the drug. Dose: 300 to 600 mg. by mouth.

(ii) Quinine hydrochloride tablet I. P. contains 300 mg. of the salt. Dose: 300 to 600 mg. by mouth.

(iii) Quinine ethyl carbonate I. P. is administered orally in the same dose as the sulfate and the hydrochloride.

(iv) Quinine dihydrochloride injection I. P. usually contains 300 mg. of the salt per ml. It can be administered by intravenous or by intramuscular injection. Dose: 300 to 600 mg.

(v) Quinine and urethane injection I. P., used as a sclerosing agent.

Therapeutic uses:

(i) **Malaria:** Discussed later.

(ii) **Myotonia congenita:** This hereditary myopathy, characterised by tonic spasm of skeletal muscles, is often benefited by 300 to 600 mg. of quinine hydrochloride given twice or thrice daily by mouth.

Other myopathies characterised by wasting and weakness of skeletal muscles do not respond to quinine. The drug has been recommended in the dose of 200 to 300 mg. before retiring to prevent nocturnal muscle cramps.

(iii) **Diagnosis of myasthenia gravis:** Quinine dihydrochloride, given orally in the dose of 600 mg. repeated at 2 hourly intervals for 3 doses, may be used for the diagnosis of myasthenia gravis when the neostigmine test proves inconclusive. Quinine accentuates the myasthenic weakness and neostigmine should be kept handy to treat the complication of respiratory paralysis.

(iv) **Analgesia and antipyresis:** Although the drug has a weaker analgesic-antipyretic activity than salicylates it is considerably more toxic. Its use as a nonspecific antipyretic should, therefore, be deplored.

(v) **As a sclerosing agent:** See Chapter 29.

4-AMINOQUINOLINES

The 4-aminoquinolines constitute the mainstay of suppressive therapy of malaria. In addition, they are useful in a variety of other conditions. The therapeutically useful compounds of this class are chloroquine, hydroxychloroquine and amodiaquine.

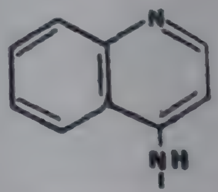

Fig. 50.1: 4-Aminoquinoline nucleus.

CHLOROQUINE: This is the most frequently used compound and is used as the diphosphate salt.

Pharmacological actions:

(a) **Antimalarial activity:** Chloroquine kills the asexual erythrocytic forms of *P. vivax* and *P. falciparum*. It is also effective against the gametocytes of *P. vivax*. It, however, has no effect on sporozoites and the persistent tissue forms. As a suppressive, chloroquine is superior to quinine and mepacrine. Resistance to chloroquine by *P. falciparum* has recently been demonstrated *in vitro* and *in vivo*. Such organisms exhibit cross-resistance to other 4-aminoquinolines and to mepacrine.

The mechanism of schizonticidal effect of the 4-aminoquinolines is not clear. The compounds have a marked affinity for nucleoproteins. It has been postulated that they may act by inhibiting the incorporation of phosphate into the RNA and the DNA of plasmodia.

(b) **Other actions:** In addition to its activity against plasmodia, the drug is effective in giardiasis, taeniasis and extraintestinal amoebiasis. It has anti-inflammatory, antihistaminic and local anaesthetic activities. Chloroquine has also a depressant effect on the myocardium and may exert a direct relaxant effect on smooth muscles when given in sufficiently large doses. *In vitro* and in large concentrations, the drug inhibits the enzyme acetylcholinesterase.

Absorption, fate and excretion: Chloroquine is rapidly and almost completely absorbed from the gastrointestinal tract. Approximately 55 per cent of the drug in plasma is bound to non-diffusible plasma constituents. The drug is highly concentrated in the liver, spleen, kidney, lung and leucocytes. The brain and the spinal cord levels, however, are only 10 to 30 times the plasma levels.

Chloroquine is degraded in the body, probably by the hepatic microsomal enzyme systems. The metabolites also exhibit antimalarial activity. Acidification of urine hastens the renal excretion of chloroquine. Because of its affinity for the tissue proteins, the drug persists in the body for a considerable time after discontinuation of medication.

Adverse reactions: Chloroquine, in general, is a relatively safe drug. Commonly it causes nausea and vomiting. The drug, however, may produce serious toxic manifestations when used in large doses for prolonged periods. The important toxic manifestations are:

(i) **Intolerance:** Skin rashes with or without pruritus, angioneurotic edema, photosensitivity and even exfoliative dermatitis have been reported. Long term treatment may lead to bleaching of the scalp hair, eyebrows and eyelashes. Abnormal blue black pigmentation of the retina may also occur with long term therapy and this may be accompanied by retinopathy. Rarely, thrombocytopenia, agranulocytosis and pancytopenia may occur.

(ii) **Eye:** Ocular complications have become commoner with the high dosage, prolonged chloroquine therapy in rheumatoid arthritis, discoid lupus and lupus erythematosus. They are uncommon during the treatment of malaria. Temporary loss of accommodation with blurring of vision or diplopia may develop during therapy. Difficulties in focussing eyes have been reported in pilots taking chloroquine prophylactically. This phenomenon is reversible on discontinuation of treatment. Lenticular opacities and subcapsular posterior cataracts have been reported. The retinal changes, collectively described as *retinopathy*, consist of constriction of the retinal arteries, retinal edema and abnormal pigmentation and depigmentation of the macula accompanied by macular degeneration. The field of vision is constricted and scotomata may appear. These changes are not reversible and need discontinuation of chloroquine treatment. Because of its prolonged sojourn in the body, the ocular changes may appear even a few years after discontinuation of chloroquine. It is recommended, therefore, that any patient on chloroquine therapy over a long period should undergo periodic ophthalmoscopic examination, with careful plotting and evaluation of visual fields. As retinopathy is probably secondary to the high concentration of chloroquine in the eye, ammonium chloride and dimercaprol have been employed to hasten its excretion. However, the usefulness of these measures has yet to be substantiated.

(iii) **Miscellaneous:** These include T wave depression in the ECG, acute psychotic episodes, seizures and rarely, neuromyopathy. Ototoxicity has been reported.

Chloroquine, administered during pregnancy, may lead to severe cochleo-vestibular defects, mental retardation and convulsions in the newborn. Intravenous use of chloroquine has caused fatalities, particularly in children, due to respiratory and cardiac arrest.

Preparations and dosage:

(i) Chloroquine phosphate tablet I.P. contains 250 mg. of the salt (150 mg. of the base). Dose: as a suppressive in acute attack: initial dose: 1 g. followed by 0.5 g. after 6 hours and 0.5 g. daily thereafter for 2 days. The comparable doses in children are, 150 mg. daily in infants, 250 to 450 mg. daily in those between 1 to 5 years and 300 to 750 mg. daily in those between 6 to 12 years. For suppressive therapy in an individual who is going into an endemic area, 0.5 g. weekly for 4 weeks.

(ii) Chloroquine sulfate tablet contains 200 mg. of chloroquine base. Dosage, same as above.

(iii) Chloroquine injection NF contains chloroquine phosphate or sulfate equivalent to 40 mg. of the base per ml. Dose: 200 to 300 mg. of the base intramuscularly, divided between two injection sites, or intravenously, slowly, diluted with 100 ml. of glucose saline. The total parenteral dose within 24 hours should not exceed 900 mg. of the base. In infants and children, the oral or parenteral dose should not exceed 5 mg. of the base per kg.

Therapeutic uses: In addition to its use in malaria, chloroquine has been used in,

(i) **Amoebiasis:** See Chapter 51.

(ii) **Giardiasis:** Chloroquine phosphate, in the dose of 250 mg. daily for 5 days or camoquin (0.6 g. single dose) is effective in this condition but mepacrine is probably the drug of choice.

(iii) **Clonorchis sinensis (Chinese liver fluke) infestation:** Chloroquine phosphate, 250 mg. daily, is given for 6 weeks.

(iv) **Taeniasis:** See Chapter 54.

(v) **Rheumatoid arthritis:** See Chapter 65.

(vi) **Discoid lupus and disseminated lupus erythematosus:** Chloroquine is useful only in the milder forms of this disease and as a supplementary therapy to corticosteroids in severely ill patients in whom the dose of adrenocortical steroids cannot be safely increased further. The arthritic and the cutaneous lesions improve markedly with chloroquine therapy. Chloroquine phosphate is given in the dose of 250 to 500 mg. daily for 1 to 4 weeks or until a clear response is obtained. The dose is then reduced to a maximum of 250 mg. and maintained subsequently.

(vii) **Miscellaneous:** Chloroquine has been successfully employed to control the acute manifestations of lepra reaction. The drug has been shown to be useful in infectious mononucleosis.

HYDROXYCHLOROQUINE: This drug, claimed to be less toxic than chloroquine, has properties similar to those of chloroquine.

AMODIAQUINE (Camoquin): This antimalarial drug is as effective as chloroquine, in a single dose. Its pharmacological actions are similar to those of chloroquine. It is rapidly absorbed on oral administration and is highly concentrated in the liver and the spleen. About 5 per cent of the total administered dose is recovered in urine while the rest is metabolised in the body. The side effects reported include gastrointestinal disturbances, headache and photosensitivity reactions. Rarely, it can cause agranulocytosis.

Amodiaquine hydrochloride I.P. is a yellow, crystalline powder bitter in taste and soluble in water.

Amodiaquine tablet I.P. contains 250 mg. of the salt. Dose: as a suppressive in an acute attack of malaria: 0.5 to 0.75 g. (0.4 to 0.6 g. of the base) on the first day and then 2 tablets daily for two days. As a suppressive in a person going into an endemic area, 0.5 g. (0.4 g. of the base) once a week.

Other indications for amodiaquine are similar to those for chloroquine.

8-AMINOQUINOLINES

PRIMAQUINE: This drug is effective against the persistent tissue forms of *P. vivax* in addition to the pre-erythrocytic and sexual forms of both *P. vivax* and *P. falciparum*. Following the administration of primaquine, only a proportion of gametocytes in the blood are destroyed, while the rest are rendered incapable of undergoing further maturation in the mosquito. The drug has a weak schizonticidal activity against *P. vivax* but exerts no effect on the schizonts of *P. falciparum*. It is, therefore, not effective as a suppressive but given along with 4-aminoquinoline, it can produce radical cure in *P. vivax* infection. Significant *in vivo* resistance to primaquine has not been reported. The mechanism of action of the 8-aminoquinolines is not definitely understood. They probably act by affecting the metabolic functions of the mitochondria in the parasite.

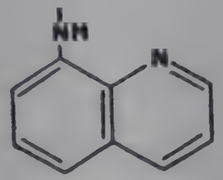

Fig. 50.2: 8-Aminoquinoline nucleus.

Absorption, fate and excretion: Primaquine and the other 8-aminoquinolines are rapidly absorbed on oral administration. The drug is concentrated in the liver; large amounts are also present in the lung, brain, heart and the skeletal muscle.

Primaquine is rapidly metabolised in the body. Only 1 per cent of the drug is excreted unchanged in the urine. The rest is inactivated probably by reduction and hydroxylation of the side chain.

Adverse reactions: Besides epigastric distress and abdominal cramps which can be minimised by taking the drug with or after food or by using antacids, the serious toxic manifestations involve the haemopoietic system. These vary from mild anemia, and leucocytosis encountered with moderate doses, to methemoglobinemia, cyanosis, leukopenia and agranulocytosis following large doses. The most significant toxic hazard is intravascular hemolysis, particularly encountered in individuals with glucose 6-phosphate dehydrogenase deficiency. The probable mechanism of this phenomenon is discussed in Chapter 32. The drug, therefore, should not be used in patients who have a tendency to granulocytopenia e.g. those suffering from rheumatoid arthritis or lupus erythematosus and in patients receiving other potentially hemolytic drugs. It should not be administered concomitantly with mepacrine or proguanil as these potentiate its toxicity.

Preparations and dosage: Primaquine tablet N.F. contains 13.17 mg. of primaquine phosphate equivalent to 7.5 mg. of primaquine base. The dose for radical cure of vivax malaria is 15 mg. daily for 15 days given along with chloroquine 1 g. on the first day and 500 mg. daily for 2 days.

Other 8-aminoquinolines: These include pentaquine and pamaquine. These agents are no longer in use, because of their higher haemopoietic toxicity in comparison to primaquine.

ACRIDINE DERIVATIVES

MEPACRINE: This drug, discovered in 1920, but used extensively only during the 2nd World War, has lost much of its importance with the discovery of chloroquine.

Mepacrine is an effective schizonticidal drug and is lethal to the sexual forms of *P. vivax*. It, however, has no action against the pre-erythrocytic and exoerythrocytic forms nor is it effective against the sexual forms of *P. falciparum*. Hence, it acts as a suppressive.

In addition to its antimalarial action, mepacrine is effective against Taeniasis and Giardiasis. It also exerts a weak quinidine like action on the myocardium and has an anti-inflammatory action. It inhibits a number of enzymes *in vitro* including acetylcholinesterase.

Absorption, fate and excretion: Mepacrine is rapidly absorbed on oral administration. It is widely distributed in the body. Because of its slow excretion, mepacrine can cause cumulation. Cumulation occurs in the liver, spleen, lungs, adrenals, kidney and the bone marrow. Significant amounts are also present in the intestinal wall, the leucocytes, the hair and the finger nails; in contrast, the levels in the CNS are negligible. An increase in the plasma pH results in an increased deposition of the drug into the tissues. It readily crosses the placental barrier.

The exact metabolic pathway of the drug is not known. Only small quantities of the drug are detected in feces and not more than 11 per cent of the oral suppressive dose of 100 mg. is detected in the urine. Alkalinization of the urine decreases and acidification increases the renal elimination of the drug. Small amounts are secreted in sweat, saliva, bile and milk.

Adverse reactions: Mepacrine, in general, is more toxic than chloroquine but acute toxic manifestations are uncommon. Nausea, vomiting and diarrhoea develop particularly with large doses given on empty stomach. Other salient adverse reactions encountered on chronic administration include urticarial and exanthematous skin rashes and yellow staining of the skin and the sclera. Other rare adverse manifestations include headache, fever, vertigo, exfoliative dermatitis and acute toxic hepatic necrosis. The drug can cause psychosis, restlessness and convulsions. Corneal edema, corneal deposits and retinopathy similar to that seen with chloroquine may occur infrequently. Aplastic anemia, leukopenia and agranulocytosis have also been reported after the use of mepacrine, but are extremely rare.

Rapid intravenous administration of mepacrine may lead to depression of the vasomotor and respiratory centres, peripheral vasodilatation, hypotension, and cardiac irregularities. The drug inhibits cholinesterase, but the role of this phenomenon in the genesis of acute toxicity is not understood.

Mepacrine should not be used in conjunction with any of the 8-aminoquinolines for the reason mentioned earlier.

Preparations and dosage:

(i) Mepacrine tablet I.P. contains 100 mg. of dihydrochloride. Dose: as a suppressive in an acute attack, 900 mg. in 3 divided doses on the first day, 600 mg. in 2 divided doses on the second day and 300 mg. daily for further 5 days. In children, the doses are proportionately smaller.

(ii) Mepacrine methanesulfonate injection N.F. is available in two strengths containing 120 or 360 mg. of the salt. It is dissolved in the requisite quantity of water for injection and administered intramuscularly divided between two sites. Dose: 120 to 360 mg.

Therapeutic uses: Mepacrine is now rarely used in malaria. Other uses are:

(i) **Taeniasis:** Discussed in Chapter 54. The drug is also effective in fish tapeworm (*D. latum*) and dwarf tapeworm (*H. nana*) infestation.

(ii) **Infestations with Giardia lamblia:** Discussed in Chapter 52.

(iii) **Trichomonas vaginalis vaginitis:** The drug is of doubtful value.

(iv) **Cutaneous leishmaniasis:** 100 mg. of mepacrine dissolved in 2 ml. of water and injected locally at the ulcer base is often useful in early stages.

(v) **Chronic discoid lupus erythematosus:** Chloroquine is usually preferred to mepacrine because of its lower toxicity.

BIGUANIDES

PROGUANIL (Chloroguanide, Paludrine): Proguanil hydrochloride, the commonly used salt of this drug, is a white, crystalline powder with a bitter taste. It is sparingly soluble in water.

Proguanil is an effective schizonticide against both *P. vivax* and *P. falciparum*. In addition, it is effective against the primary pre-erythrocytic forms of *P. falciparum*. The drug is not directly gametocidal but prevents the development of gametes, encysted in the gut wall of the mosquito. It has, however, no action against the persistent tissue forms of *P. vivax* and its suppressive action is slower than that of the 4-aminoquinolines. West African strains of *P. falciparum* are usually *genetically resistant* to proguanil while all the varieties of plasmodia have been demonstrated to develop an *acquired resistance* to this agent. This phenomenon has considerably reduced the utility of proguanil.

Proguanil has negligible antiplasmodial action *in vitro*. Its antimalarial action *in vivo* is attributed to its conversion into a cyclic ring triazine metabolite in the human body. This active antimalarial form of proguanil is postulated to act by preventing the reduction of folic acid by the plasmodia. This, in turn, interferes with the nucleic acid synthesis, causing arrest in erythrocytic schizogony. As the sulfonamides prevent the conversion of PABA into folic acid, they synergize with the antimalarial effect of proguanil. The postulated mechanism of action of proguanil also explains the development of resistance to its action by the plasmodia and its potential bone marrow toxicity when used in large doses. Although it is a biguanide derivative, proguanil has no hypoglycemic action.

Absorption, fate and excretion: Proguanil, when given orally, is slowly but adequately absorbed, mostly from the small intestine. The drug does not accumulate in the tissues significantly but achieves a higher concentration within erythrocytes than in plasma. Approximately 75 per cent of the plasma proguanil is bound to proteins.

Proguanil is rapidly excreted from the body, mainly in the urine.

Adverse reactions: Proguanil is free from significant toxic effects when used in therapeutic doses. Gastrointestinal disturbances may develop occasionally.

When used in large doses, proguanil significantly reduces the volume and the acidity of the gastric juice in response to histamine and depresses the myocardium. The drug may rarely cause hematuria and appearance of casts and epithelial cells in urine. A reduction in the leucocyte count may be seen with large doses.

Preparations and dosage: Proguanil tablets contain 25, 100 or 300 mg. of the hydrochloride. The base content of the salt is approximately 87 per cent. Dose: as a suppressive in an acute attack, 300 to 600 mg. initially, followed by 300 mg. daily for 5 days. It is not a drug of choice for controlling an acute attack. For causal prophylaxis, a dose of 100 to 200 mg. daily is used depending upon the sensitivity of the strain prevalent in the particular area.

CHLORPROGUANIL: This drug, similar to proguanil in its antimalarial action, has a longer duration of action, extending over 4 days. As a causal prophylactic, the drug is used in the dose of 20 mg. weekly. It is not recommended for relief of an acute attack. The drug exhibits cross resistance with proguanil.

CYCLOGUANIL PALMOATE (C1-501; As-Triazine, Camolar): This drug resembles the dihydrotriazine derivative of proguanil. Given as a suspension in oil intramuscularly, in the dose of 5 mg. per kg., it provides protection from both *P. vivax* and *P. falciparum* for 3 months or longer. The prolonged period of protection is due to slow release of the active moiety from the repository preparation. The low plasma levels of the active drug prevent the growth as well as the survival of the pre-erythrocytic and erythrocytic parasites. The possible disadvantages of the drug are development of resistant strains and secondary folic acid deficiency.

DIAMINOPYRIMIDINES

PYRIMETHAMINE (Daraprim): This drug has an effective schizonticidal action mainly against *P. vivax*. It is also effective against the pre-erythrocytic forms, particularly those of *P. falciparum*. The drug is not gametocidal, but like proguanil, it prevents the maturation of the fertilized encysted gamete within the mosquito. It is selectively toxic to malaria parasites as it binds the dihydrofolate reductase of the parasite without affecting the corresponding enzyme in the mammalian host. The drug is more potent than proguanil. Development of resistance to the drug *in vivo* has been reported and some degree of cross-resistance between pyrimethamine and proguanil has also been observed. This is probably because of a common mechanism of action of the two drugs and the structural similarity between pyrimethamine and the active dihydrotriazine metabolite of proguanil. The antimalarial activity of the drug is enhanced when used in conjunction with sulfonamides.

Absorption, fate and excretion: Pyrimethamine is adequately but incompletely absorbed from the small intestine. The drug is slowly excreted by the kidney, only about 20 per cent of the drug appearing in the urine in the free form. Its plasma half-life is about 96 hours.

Adverse reactions: When used in therapeutic doses, the drug is relatively safe. Megaloblastic anemia, resembling that due to folic acid deficiency, may develop when the drug is used in large doses. Thrombocytopenia and agranulocytosis are occasionally seen. These respond to the oral administration of folinic acid.

Preparations and dosage: Pyrimethamine is dispensed as a 25 mg. tablet. Dose: as a causal prophylactic, 25 mg. once a week. For relief of an acute attack of *P. vivax* 50 mg. on the first day followed by 25 mg. daily for 2 days. It is however, not the drug of choice in acute attack.

Therapeutic uses: In addition to its use in malaria, pyrimethamine is recommended in adults suffering from toxoplasmosis, in the dose of 25 mg. twice daily followed by 25 mg. daily for 1 month along with sulfadiazine, 4 g. daily for 1 month. Loading doses of 50 to 100 mg. of pyrimethamine may be used in the event of ocular complications. In infants and children, a dose of 1-2 mg. per kg. is recommended. The total daily dose, however, should not exceed 25 mg. It is also used in the treatment of polycythemia vera.

MISCELLANEOUS DRUGS

MEFLOQUINE is a quinoline-methanol compound. Given orally as a single dose, it is highly effective against *P. falciparum* including the strains resistant to chloroquine. It can be combined with quinine in severe cases. The drug may cause abdominal pain, dizziness, nausea and vomiting. It has also been used for chemoprophylaxis and is under evaluation.

The sulfonamides are known to have antimalarial activity, and sulfadiazine, along with pyrimethamine, can be effectively used when neither drug alone is effective, against *P. falciparum* resistant to chloroquine or pyrimethamine. A long acting sulfonamide such as sulfadoxine (half life 200 hours) is usually preferred.

The sulfones, particularly D.D.S., have been used in the dose of 25 mg. daily for 4 weeks from the 7th day of illness onwards, in combination with quinine and pyrimethamine, to prevent recrudescence in chloroquine-resistant falciparum malaria. D.D.S. has been used in the same dose, along with chloroquine, pyrimethamine or quinine, to prevent recrudescence of *P. falciparum* infection in non-immune American troops deployed in Viet-Nam.

MANAGEMENT OF MALARIA

Prophylaxis: If a person is residing in an area where malaria is endemic, radical cure should not be attempted as the chances of reinfection are high. He should be given any of the following drugs to prevent an acute attack (suppressive therapy):

(a) Chloroquine phosphate—250 mg. tablet. 2 tablets (equivalent to 300 mg. of the base) once a week.

(b) Amodiaquine hydrochloride—500 mg.

(equivalent to 400 mg. of the base) once a week.

(c) Pyrimethamine—1 or 2 tablets of 25 mg. per week.

(d) Proguanil hydrochloride—100 mg. (1 tablet) daily. A drug of second choice.

(e) Mepacrine hydrochloride—100 mg. daily.

(f) Quinine sulfate or dihydrochloride: 650 mg. daily.

The last two drugs are indicated only when other agents are not available. In areas where malaria is highly endemic and exposure to infection is heavy, the dose of chloroquine or amodiaquine may have to be doubled.

(g) Combination of pyrimethamine with sulfadoxine has been highly effective in preventing malaria when administered every 1-2 weeks. It is mainly recommended for prophylaxis of chloroquine resistant falciparum malaria.

Treatment of an acute attack: The drugs used in acute clinical attack are:

(a) Chloroquine phosphate: The drug usually ensures a radical cure of *P. falciparum malaria.* For *P. vivax* malaria, freedom from further clinical attacks should be maintained by giving 300 mg. of the base weekly.

(b) Amodiaquine hydrochloride: This acts equally well at a dose level lower than chloroquine.

(c) Mepacrine hydrochloride: This drug is now rarely used.

(d) Quinine hydrochloride or sulfate: Initial dose 650 mg. followed by 650 mg. after 6 hours and again 8 hours after the second dose, followed by 650 mg. twice daily for a further period of 3 days.

In patients with chloroquine-resistant falciparum malaria a short course of quinine for 2-3 days, followed by a single dose of pyrimethamine 75 mg. together with sulfadoxine 1.5 g, gives high cure rates. Quinine alone is often followed by recrudescence. Another promising combination under investigation is that of quinine with mefloquine.

Tetracycline alone is a weak antimalarial drug. But the experience of the Indian Armed Forces suggests that quinine plus tetracycline is highly effective in chloroquine resistant *P. falciparum* cases.

Cerebral malaria and severe infections: Although the treament of acute attacks with oral therapy is satisfactory in majority of the cases, in severe *P. falciparum* infection leading to cerebral malaria or associated with cerebral symptoms, nausea and vomiting, parenteral antimalarial therapy may be necessary. Quinine and chloroquine are the most suitable drugs for parenteral administration. Intravenous injection acts somewhat more rapidly than intramuscular injection but presents a greater risk of toxicity, particularly with quinine. Quinine probably acts more quickly than chloroquine.

Intravenous quinine hydrochloride is given by infusion in the dose of 5 to 10 mg. per kg. diluted in normal saline with 5 per cent glucose, over 3-4 hours. This may be repeated, if necessary, after 6 to 8 hours. The dose should not exceed 20 mg/kg within 24 hours. At present, intravenous quinine is the only regime available that is effective in seriously ill patients with chloroquine resistant falciparum malaria. The patient is subsequently put on oral quinine 650 mg. thrice daily and the treatment is continued for 12 days.

Chloroquine is usually preferred to quinine because of its relative safety, in areas where sensitive strains are prevalent. The intravenous dose of the base, given either as diphosphate, sulfate or hydrochloride, is 200 mg. given preferably through a glucose saline drip.

Mepacrine methanesulfonate may be administered intramuscularly in the dose of 300 mg. at 6 hourly interval if both quinine and chloroquine are not available.

Radical cure: Radical cure should be aimed at only in infections occurring in a nonendemic area. Such a patient should receive primaquine in the dose of 7.5 mg. of the base daily for 2 weeks. Simultaneously, he should continue to receive 300 mg. of the chloroquine base weekly for suppression of an overt attack. Primaquine therapy is essential mainly in vivax malaria as falciparum malaria is completely cured by any of the schizonticidal agents used alone.

Adjuvant therapy in malaria: Cerebral malaria sometimes causes coma and shock. Blood pressure should be maintained by intravenous fluids and noradrenaline. Management of coma is similar to that of coma due to other causes. However, in some cases, lumbar puncture to reduce intracranial tension and use of i.v. glucocorticoids may cause dramatic recovery. Convulsions should be treated with parenteral diazepam.

Severe malaria can sometimes cause renal failure leading to oliguria, anuria and death due to uremia. In the initial stages, the osmotic diuretic mannitol may be useful. However, later hemodialysis or peritoneal dialysis can be a life saving measure. It is also important to remember the possibility of such a complication, since administration of excess parenteral fluids during the period of unrecognized renal impairment can precipitate acute water intoxication and fatal pulmonary edema.

Chronic malaria is usually associated with iron deficiency anemia, which responds to oral iron therapy. In severe anemia, parenteral iron and even blood transfusion may be necessary.

Immunity in malaria: Development of partial immunity is now a recognized fact in *P. falciparum* infection. The immunity is basically humoral, associated with the gamma globulin fraction. Immune antibodies cross the placental barrier and confer passive immunity on the foetus. The latter, therefore, is protected for some months after birth. The immunity operates against the erythrocytic stage of the parasite, but is ineffective against the primary pre-erythrocytic, sexual and persistent tissue forms of the parasite. Again, immunity in malaria is not only species-specific, but to some extent also strain-specific. Thus, a person who has developed immunity to a *P. falciparum* strain in a particular area may get infected with a different strain when in another area. The immunity is not absolute and can diminish substantially when an immune adult moves for a year or more to a nonendemic area.

Malaria eradication: This concept is based on the idea of completely eliminating the disease from a particular area so as to halt its transmission completely, at the same time, preventing the reintroduction of the disease from outside. Malaria eradication, therefore, envisages a vigorous attack on the parasites in human patients with the suppressive, causal prophylactic and radical curative drugs, along with eradication of the vector mosquitoes. The latter includes the use of various insecticides and larvicides such as D.D.T. and organophosphorous compounds.

Mosquito repellents: It is extremely difficult to ensure 100 per cent protection from the hungry Anopheles mosquitoes. A simple remedy which acts as mosquito repellent, by its smell has the following composition:

Cedar wood oil	.. 18 ml.
Citronella oil	.. 42 ml.
Spirit of camphor	to 100 ml.

Citronella oil can also be applied in the form of vanishing cream. It is nonirritant, nontoxic, cheap and not so unpleasant. Probably more effective is a 35 per cent emulsion of dimethyl phthalate which acts as an irritant to insect's feet. The difficulty about this drug is that it must be rubbed into every part, avoiding eyelids, lips and scrotum. Other agents used are ethohexadiol, butopyronoxyl, diethyltoluamide and n-butyl acetanilide. These are also irritant to the mucous membrane and eyes and have an intensely bitter taste. Sensitivity reactions may occasionally develop with their use.

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Chemotherapy of Amoebiasis

Amoebiasis is an infectious disease caused by the protozoon, *Entamoeba histolytica*. The disease, though labelled as 'tropical', is not uncommon in temperate zones; its incidence in U.K. and U.S.A. is estimated to be about 10 per cent. It primarily affects the colon, but other organs like liver, lung and brain may get secondarily involved. The disease is characterised by gastrointestinal and constitutional symptoms and has a tendency to chronicity. Acute amoebic dysentery is associated with bloody, mucoid stools, abdominal pain and tenesmus. Chronic amoebiasis usually presents with vague symptoms like anorexia, abdominal pain and intermittent diarrhoea or constipation. There may be tenderness over the caecal region. Many infected persons, who pass the cystic forms of the protozoan in feces, however, may remain completely symptomless and act as 'carriers'.

E. histolytica usually lives as a harmless commensal in the lumen of human bowel, a state which might be termed asymptomatic amoebiasis. The parasite subsists on debris and bacteria and not on the tissues of its host. When it becomes a pathogen, the trophozoites become larger and hematophagous, having many erythrocytes in the endoplasm and cause invasive amoebiasis.

Intestinal amoebiasis results in ulceration of the colon. The regions involved in descending order of frequency are the caecum, ascending colon and the recto-sigmoidal area. In fatal cases, the entire colon and even the terminal portion of the ileum may be involved. A granulomatus lesion of the caecum giving rise to a lump in that region, known as amoeboma may cause a clinical attack of appendicitis. The incidence of invasive amoebiasis is higher where sanitation and living conditions are poor.

Life cycle of E. histolytica: *E. histolytica* exists in two forms: the trophozoites, present in infected tissues, and the cysts, which develop from the trophozoites on the surface of the colonic mucosa. The trophozoites exhibit amoeboid movements and constitute the active form of the parasite. The cysts represent a dormant stage which enables the organism to survive unfavourable environmental conditions. The cysts are resistant to freezing and partial drying and transmit infection from person to person.

Cysts are usually ingested following fecal contamination of water or food. Bad hygiene and insects like flies assist in the propagation of infection. In the intestine of the host, the cyst wall is weakened by the intestinal enzymes and the trophozoites released invade the walls of the colon. The organism may then find its way to the liver and other tissues, giving rise to extra intestinal amoebiasis.

The drugs used in chemotherapy of amoebiasis may be classified clinically as follows:

I. Drugs used only in intestinal amoebiasis: Emetine bismuth iodide, halogenated oxyquinolines, pentavalent organic arsenicals, antibiotics, diloxanide furoate, chlorphenoxamide and kurchi.

II. Drugs used in both intestinal and extraintestinal amoebiasis: Emetine, dehydroemetine, metronidazole, phanquone.

III. Drugs used only in extraintestinal amoebiasis: Chloroquine.

An alternative chemical classification is:

I. Emetine group e.g.: Emetine, dehydroemetine and its resinate, emetine bismuth iodide.

II. Quinoline derivatives:

(a) Halogenated hydroxyquinolines: Diiodohydroxyquinoline, iodochlorohydroxyquinoline, chiniofon sodium, broxyquinoline, chlorohydroxyquinoline.

(b) 4-aminoquinolines: Chloroquine, amodiaquine.

III. Organic arsenicals: Carbarsone and glycobiarsol.

IV. Antibiotics: Tetracyclines, paromomycin, fumagillin.

V. Miscellaneous: Diloxanide furoate, chlorphenoxamide, niridazole, metronidazole, phanquone and kurchi.

EMETINE GROUP

EMETINE: Emetine is an alkaloid obtained from ipecac, the root of the plant *Cephalis ipecacuanha.* The other alkaloid, cephaeline, though amoebicidal, is too toxic for therapeutic use.

Antiamoebic action: Emetine has a direct lethal effect on the trophozoites of *E. histolytica.* It has, however, little effect on the cystic forms. Trophozoites affected by emetine show degeneration of the nucleus and reticulation of the cytoplasm. This arrests their multiplication and leads to their eventual phagocytosis. Resistance to emetine *in vitro* or *in vivo* has not been reported. The other pharmacological actions of the drug are mainly important from the point of view of its toxicity and are discussed below.

Absorption, fate and excretion: Emetine has a bitter taste and is absorbed from the gut but because of its irritant nature, it is administered by deep intramuscular injection. The drug gets highly concentrated in the liver. Significant amounts are also present in the lung, kidney and spleen. The drug is slowly excreted in urine and hence, repeated injections can lead to cumulative toxicity.

Adverse reactions: The major drawback of emetine is its high toxicity. The adverse reactions to emetine are:

(i) **Local reactions:** These often appear when emetine is administered subcutaneously but are uncommon when the drug is given by deep intramuscular injection. It may cause local pain, tenderness, stiffness and weakness of the muscles and rarely an abscess. Local eczematous lesions and rarely, generalized urticarial and purpuric lesions have been encountered.

(ii) **Gastrointestinal disturbances:** These though common with oral therapy, are also observed with parenteral therapy. Occurrence of nausea, vomiting, diarrhoea, headache, dizziness and prostration may confuse the picture of amoebic colitis. Although diarrhoea is secondary to the direct irritant action of emetine on intestines, vomiting occurs both as a result of gastric irritation and stimulation of the chemoreceptor trigger zone.

(iii) **Cardiovascular system:** The most important adverse effects of emetine are cardiovascular. The drug can cause tachycardia, precordial pain, hypotension, myocarditis and pericarditis. The ECG offers a sensitive and early index of cardiotoxicity. The changes described include lowering and inversion of T-wave, deformation of ST segment and QRS complex, prolongation of PR and QT intervals, atrial tachycardia and/or premature beats.

To avoid emetine cardiotoxicity, it is advisable to confine the patient to bed during emetine therapy and to avoid undue exertion for three weeks thereafter. It is necessary to observe the pulse rate and blood pressure during the therapy; ideally, an ECG should be taken before starting the therapy, repeated after the 5th dose and again after a week.

(iv) **Miscellaneous:** The drug may occasionally cause peripheral neuritis.

As far as possible, the drug should be avoided in patients with cardiac or renal damage, in pregnant women, in old people and in young children.

Preparations and dosage:

(i) Emetine hydrochloride injection I.P. contains 60 mg. of the salt per ml. Dose: 30 to 60 mg. daily by subcutaneous or deep intramuscular injection.

(ii) Ipecacuanha liquid extract I.P. and Ipecacuanha tincture I.P. are occasionally used as emetics in the dose of 0.6 to 2 ml. and 6 to 20 ml. respectively.

Therapeutic uses: Besides its use in amoebiasis, emetine is used in *Paragonimus westermanii* (lung fluke) infestation, in the dose of 1 mg. per kg. daily parenterally for 12 days. In the form of ipecacuanha, it was used as an emetic. The use of emetics in the treatment of poisoning is discussed elsewhere.

DEHYDROEMETINE: This is a semi-synthetic drug claimed to be less toxic than emetine, has similar toxicity and applications. (i) Dehydroemetine resinate is a slow release preparation given orally. Dose: 50 mg. daily for 10 days.

(ii) Dehydroemetine injection NF contains 60 mg. of the drug per ml. Dose: 1 mg. per kg. of body weight intramuscularly daily for 6 to 10 days. In addition, the drug, given in the dose of 4.5 mg. per kg. orally for 4 weeks, has shown a beneficial effect in giardiasis and cutaneous leishmaniasis.

EMETINE BISMUTH IODIDE: This drug contains 25 per cent by weight of anhydrous emetine and 20 per cent bismuth. The latter may contribute a mild astringent effect while iodide probably enhances the amoebicidal action of emetine. The main advantage of the compound is its efficacy by mouth. It acts partly by releasing emetine in the intestine and in addition, has an independent amoebicidal activity *in vivo*. The drug shares the adverse effects of emetine. Prominent among these are nausea, colic, diarrhoea and cardiotoxicity. Iodism may develop occasionally. To minimise the gastrointestinal and cardiac disturbances, the patient should be kept in bed for at least 2 days at the initiation of therapy. Administration of a barbiturate 10 to 15 minutes before the drug considerably reduces the gastrointestinal disturbances.

Emetine bismuth iodide is a reddish orange, insoluble powder with a bitter taste. Emetine bismuth iodide tablet NF contains 60 mg. of the drug. The tablet is enteric coated. Dose: 60 to 200 mg. daily after the evening meal, for 12 days.

QUINOLINE DERIVATIVES

Amongst these, diiodohydroxyquinoline, iodochlorohydroxyquinoline, broxyquinoline, chlorhydroxyquinoline and chiniofon sodium are halogenated oxyquinolines while chloroquine is a 4-aminoquinoline derivative. All the halogenated oxyquinolines also have weak antibacterial and antifungal properties.

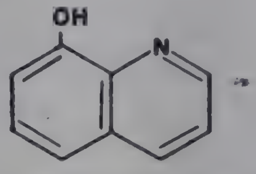
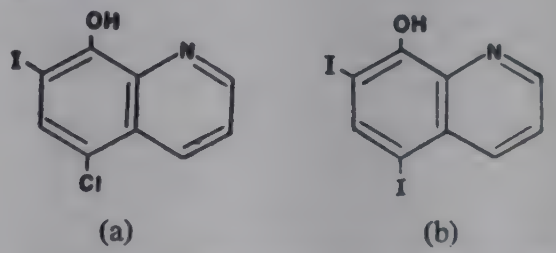


Fig. 51.1: Hydroxyquinoline nucleus.

The mechanism of action of halogenated oxyquinolines is unknown. They are believed to interfere with the essential enzyme systems of the parasite or to halogenate its proteins.



(a) (b)

Fig. 51.2: (a) Iodochlorohydroxyquinoline.
(b) Di-iodohydroxyquinoline.

DIIODOHYDROXYQUINOLINE (Diodoquin): This halogenated quinoline (Fig. 51.2) is an effective amoebicide, being effective against both motile and cystic forms of the protozoan, more so against the former. Clearance of cysts partially occurs secondary to elimination of trophozoites. It is, however, ineffective in extraintestinal amoebiasis.

Absorption, fate and excretion: Diiodohydroxyquinoline is insignificantly absorbed from the gastrointestinal tract and most of the drug is detected in feces on oral administration. The antiamoebic activity of the drug, therefore, is purely of local nature.

Adverse reactions: These, in general, are mild and uncommon. The drug may occasionally cause nausea, vomiting and diarrhoea. Chills, fever, skin eruptions and furunculosis (iodine dermatitis) have been reported. Headache and vertigo develop occasionally. In animals, the drug can produce hepatic damage but this is rare in humans. It is contraindicated in patients with iodine intolerance.

Preparations and dosage:

Diiodohydroxyquinoline tablet NF contains 300 mg. of the drug. Dose: 600 mg. thrice daily for 20 days. Another course may be given after 2 to 3 weeks. In infants, the drug is given in the daily dose of 50 to 100 mg. thrice daily; in children between 1 to 5 years, 150 to 300 mg. 2 or 3 times daily and in those between 6 to 12 years, 300 mg. thrice daily. Because of its relative insolubility in water, the drug cannot be given as a retention enema.

IODOCHLOROHYDROXYQUINOLINE or QUINIODOCHLOR (Vioform): This drug which resembles diiodohydroxyquinoline in antiamoebic action, is probably more useful in chronic cyst-carriers than in the treatment of acute amoebic dysentery. The drug is not much absorbed from the gastrointestinal tract and owes its antiamoebic action probably to a local effect. It also has an antifungal action.

The adverse effects are usually mild and include diarrhoea or constipation, abdominal pain, anal pruritus and mild iodism. A neurological syndrome consisting of myelitis, peripheral neuritis and sometimes optic nerve involvement (Subacute Myelo-optic Neuropathy—SMON) has been reported in patients receiving hydroxyquinoline derivatives over prolonged periods. These cases are mostly reported from Japan. Many symptoms can improve following the stoppage of the drug though residual disease can remain and deaths have been reported. Usually, oral daily doses of 750 mg. for 2 weeks or less are considered relatively safe in adults. Patients receiving daily doses of over 1500 mg. need careful monitoring since with high doses, symptoms can occur as early as the fifth day of the therapy.

Iodochlorohydroxyquinoline I.P. is available as tablets containing 250 mg. of the drug. Dose: 750 mg. daily in 3 divided doses for 10 days. The course may be repeated after a week. It may be used along with emetine or alternated with other drugs. The drug can also be given as a retention enema. It is prepared by suspending 2 g. of the drug in 200 ml. of water. It is instilled on alternate nights for a total of 5 instillations.

Iodochlorohydroxyquinoline cream contains 3 per cent of the drug and is used topically in fungal infections of the skin.

Therapeutic uses: Besides its use in amoebiasis, the drug is used as a suppository or insufflation in vaginitis due to *Trichomonas vaginalis* and in leucorrhoea, secondary to moniliasis and mixed bacterial infections. A combination of systemic and local therapy usually achieves better results. A disadvantage of topical application is yellow staining of clothes and linen.

CHINIOFON SODIUM: This drug is now rarely used in therapeutics. For details, see the previous edition of this book.

BROXYQUINOLINE (Intestopan): This is a bromo derivative of hydroxyquinoline with similar properties as other hydroxyquinolines. It does not seem to possess any advantage over other well established drugs.

CHLORHYDROXYQUINOLINE (Halquinol, Quixaline). This is another quinoline derivative administered in the dose of 0.25 to 0.5 g., 3-4 times daily. It has similar actions as other quinoline compounds.

CHLOROQUINE: The pharmacology of chloroquine is discussed in Chapter 50. Given orally, it is completely absorbed and hence, has a minimal direct amoebicidal action in the intestine. It is, therefore, not useful in intestinal amoebiasis.

However, its selective concentration in liver has made it a valuable drug in the treatment of amoebic hepatitis. It is also useful in amoebic infection of the lung. The drug is probably less effective and slower acting than emetine but is safer than the latter. As the drug has no effect against the intestinal forms of the protozoan, an intestinal amoebicide should be given concurrently.

Chloroquine treatment can also be used as a diagnostic test in suspected cases of amoebic hepatitis and it is often combined prophylactically with an intestinal amoebicide in the treatment of acute amoebic dysentery.

ORGANIC ARSENICALS

CARBARSONE: This pentavalent organic arsenical compound, effective against both motile forms and cysts, owes its antiamoebic action probably to inhibition of sulfhydryl enzyme systems of the parasite. It is believed to act only after reduction into a trivalent compound. It is of no value in extra-intestinal amoebiasis. It is now rarely used even in intestinal amoebiasis.

The adverse effects reported include gastrointestinal disturbances, skin rashes and arsenic intoxication (see Chapter 66).

Carbarsone tablet NF contains 250 mg. of the drug. Dose: 500 mg. daily in 2 divided doses for 10 days. Another course may be repeated after a rest period of 10 days. The drug may also be used as an insufflation in *Trichomonas vaginalis* vaginitis.

GLYCOBIARSOL (Milibis): This pentavalent arsenical is absorbed to a smaller extent from the gastrointestinal tract than carbarsone. The drug shares the toxic effects of carbarsone.

Glycobiarsol I.P. contains 14 to 16 per cent of pentavalent arsenic and 36 to 42 per cent of bismuth. Bismuth may be responsible for the mild astringent and antidiarrhoeal effect of the compound.

Glycobiarsol tablet I.P. usually contains 500 mg. of the drug; dose: 500 mg. thrice daily for 10 days.

Glycobiarsol suppository containing 250 mg. of the drug is used in the treatment of trichomonal and monilial vaginitis.

ANTIAMOEBIC ANTIBIOTICS

TETRACYCLINES: The intestinal bacteria are essential for the production of intestinal amoebic lesions. They probably act by creating an environment congenial to the growth of amoebae, by manufacturing certain metabolites and vitamins on which the protozoa thrive, and by producing secondary infection. The tetracyclines, though exhibiting an antiamoebic action *in vitro* in large doses, probably act *in vivo* by altering the intestinal bacterial flora and creating a medium unfavourable for the growth of amoebae. They may be administered in the dose of 0.25 g. 6 hourly for 15-20 days, as an alternative to metronidazole in amoebic dysentery. It is a pure lumenal amebicide. The return of the bacterial flora to pretreatment level may lead to a relapse.

PAROMOMYCIN (Humatin): This antibiotic, discussed elsewhere in detail, has been found to be effective in both acute and chronic amoebic dysentery, when administered orally daily in the dose of 25 mg. per kg. in divided doses, for 5 days. It is not significantly absorbed when given orally and is of no value in extraintestinal amoebiasis. The drug is less effective than emetine in the treatment of acute cases. It is, however, useful in the treatment of taeniasis (See Chapt. 54).

FUMAGILLIN: This antibiotic, derived from *Aspergillus fumigatus*, is effective against both the vegetative and the cystic forms of *E. histolytica*. It, however, does not affect fungi or bacteria. The drug is of no value in extraintestinal amoebiasis. Re-

Resistance by amoebae to this antibiotic has not been reported.

The adverse effects include skin eruptions, sometimes with desquamation, headache, vertigo, muscular pains, gastrointestinal disturbances and granulocytopenia. Because of its toxicity, it is no more used.

MISCELLANEOUS AGENTS

DILOXANIDE FUROATE (Furamide): This potent direct amoebicidal drug is mainly effective in chronic intestinal amoebiasis, in cyst passers and partially useful in acute cases. It is, however, of no value in extraintestinal amoebiasis.

In experimental animals diloxanide furoate is absorbed to the extent of 70 to 90 per cent when given orally. Approximately 60 to 90 per cent of the oral dose is detected in urine within 48 hours.

Diloxanide furoate has been found to be relatively non-toxic. The adverse effects reported so far include gastrointestinal disturbances, particularly flatulence and skin rashes.

Diloxanide furoate is available as 500 mg. tablet and is administered orally in the dose of 500 mg. 3 times daily for 10 days. As the drug is non-cumulative, a second course may be given immediately following the first course.

CHLORPHENOXAMINE (Mebinol): This drug, given in the dose of 500 mg. thrice daily for 8 days is claimed to eradicate the cysts. The drug is of limited value in the treatment of acute and subacute amoebiasis and not effective in extraintestinal forms of the disease.

NIRIDAZOLE (Ambilhar): This drug, effective in schistosomiasis, has been tried in the treatment of acute amoebic dysentery and in patients with amoebic liver abscess. Though the drug is beneficial in both intestinal and hepatic amoebiasis, the toxic manifestations, namely, gastrointestinal disturbances, insomnia, headache, dizziness, epistaxis, epilepsy, and notably psychosis, have precluded its routine use in therapeutics. It can also produce ECG changes similar to emetine. The drug has been shown to interfere with spermatogenesis in animals. It has also been reported to cause hemolysis in G6PD deficient individuals. It appears to have immunosuppressive properties and prolongs the skin homograft survival. The drug colours the urine red and patients should be warned about this. Use of niridazole in guinea worm infestation is described in Chapter 54.

METRONIDAZOLE (Flagyl, Unimezol, Metrogyl): Metronidazole is a useful addition in the therapy of protozoal diseases. It is a potent *in vitro* amoebicide. Unlike most other amoebicidal drugs, metronidazole is effective in all clinical forms of amoebiasis. Its relative freedom from toxicity makes it a valuable drug in those patients in whom emetine is contraindicated. In general, larger doses are required in intestinal amoebiasis (especially in acute amoebic dysentery) than in hepatic amoebiasis. Its pharmacology is discussed in Chapter 52.

PHANQUONE (Entobex): This drug has antiamoebic and antibacterial properties. It is absorbed from the intestines and excreted in active form in the bile and in the urine. The drug is effective against both intestinal and extraintestinal amoebiasis. The adverse effects include gastrointestinal disturbances and dizziness. These can be avoided by taking the drug with meals. After administration of the drug, the urine assumes a dark yellow colour owing to the presence of excretory products. It has been used as an alternative to emetine bismuth iodide and to supplement emetine hydrochloride in the treatment of acute and chronic amoebiasis and hepatic amoebiasis. The usual dosage is 150 to 300 mg. daily in divided doses for 5 to 10 days. The course may be repeated after a minimum interval of 2 weeks. It is available as 50 mg. tablets.

KURCHI: Kurchi consists of the dried

stem bark of *Holarrhena antidysenterica*. The alkaloid content of the bark is approximately 2 per cent. Kurchi has mild antiamoebic activity and is useful only in intestinal amoebiasis.

Kurchi liquid extract I.P. containing 1 per cent w/v of the total alkaloids of kurchi is occasionally used in mixtures for mild amoebiasis in the dose of 8 to 16 ml. Kurchi bismuth iodide I.P., containing 23 to 27 per cent of the total alkaloids and 18 to 24 per cent of bismuth, may be used instead in the dose of 300 to 600 mg. by mouth. It produces mild toxicity mainly nausea and vomiting.

MANAGEMENT OF AMOEBIASIS

Amoebiasis, in general, is a difficult disease to treat because of its tendency to chronicity and the inability of various drugs to eradicate the cystic froms of the parasite completely. Further, drugs like emetine are potentially toxic.

The diagnosis of intestinal amoebiasis without demonstration of trophozoites in stools is rarely justified. This form is most readily found in diarrhoeal stools and a saline purgative is often necessary to induce diarrhoea in cases with vague symptoms. Examination of the swab obtained on sigmoidoscopic examination is useful in clinching the diagnosis. The stools should be examined promptly. It is important to distinguish the trophozoites from macrophages and even experts may find it difficult to identify an active amoeba as *E. histolytica* when it is seen without a typical amoebic exudate and engulfed red blood cells.

Cysts are usually found in formed stools. However, the period of their formation varies considerably in different individuals. Their identification again requires considerable patience and experience. A casual failure to identify cysts does not, therefore, exclude the presence of amoebiasis and repeated stool examination is necessary.

The administration of antimicrobial agents like sulfonamides and tetracyclines greatly increases the difficulty of detecting *E. histolytica*. Empiric treatment of diarrhoea with these agents, therefore, is not advocated. Mineral oil and barium also interfere in the detection of trophozoite.

In the presence of symptoms of hepatitis, demonstration of *E. histolytica* in stools aids the diagnosis. This is often not possible, particularly if the patient has received antimicrobial therapy empirically for fever. The complement fixation test is positive in a high proportion of cases of liver abscess but is rarely positive in asymptomatic cyst carriers. If the patient with hepatitis is acutely ill, it is justifiable to carry out a therapeutic test with emetine or metronidazole, purely on clinical diagnosis.

Acute intestinal amoebiasis: Emetine is the most valuable agent for rapidly controlling the symptoms of severe infection. However, its value is limited by its toxicity and its inability to eradicate cysts, unless combined with a lumenal amoebicide.

The acutely ill patient should receive emetine hydrochloride or dehydroemetine in the dose of 1 mg. per kg. (60 mg. in an adult) by deep intramuscular injection with the precautions mentioned previously. The drug should be divided into two doses on the first day so as to detect any idiosyncratic manifestations. Treatment with emetine should be continued till adequate symptomatic relief is achieved; this usually takes 3 to 4 days. However, treatment should not be continued beyond 5 days to avoid the cardiotoxicity of the drug. Emetine treatment should be followed by emetine bismuth iodide 200 mg. daily or diloxanide furoate, 1.5 g. daily for 10 days or by di-iodohydroxyquinoline or iodochlorohydroxyquinoline 600 mg thrice daily or 250 mg. thrice daily respectively for 15 days. Some authorities, in addition, give 1 g. of tetracycline daily in 4 divided doses for 7-10 days; this however, is unnecessary in most of the cases.

Metronidazole in the dose of 600-800

mg. three times a day for five days is a preferred substitute for emetine in this condition. It is less toxic and effective orally. Further advantage of this drug is its effectiveness in hepatic amebiasis which can never be entirely excluded in any case of amoebic dysentery.

Adjuvant therapy includes the use of binding mixtures containing astringents, kaolin and antispasmodics for relief of pain and diarrhoea and correction of dehydration in severe cases. A cardiac lesion should be excluded before starting with emetine and strict bed rest should be enforced during its use. None of the treatment regimens give entirely satisfactory results and relapse may occur even after apparent cure at 28 days.

Chronic intestinal amoebiasis: These patients do not have many parasites in the lumen of the intestines and therefore, require drugs capable of destroying the trophozoites at their location. It is not necessary to kill the cysts because they are eliminated in the feces. The drug regimen advocated in such cases is emetine bismuth iodide 200 mg. daily or dehydroemetine resinate 5 g. daily for 10 days. Diloxanide furoate is a safer substitute given in the dose of 500 mg. 3 times daily for 10 days. Other authorities advocate a combination of di-iodohydroxyquinoline 1.8 g. daily and tetracycline 1 g. daily for 10 days along with chloroquine, 600 mg. of the base daily for 2 weeks. Chloroquine is believed to protect the liver. However, its necessity in the absence of liver involvement is controversial. Repeated administration of commercial preparations containing tetracyclines should be avoided for fear of development of drug resistant Enterobacteria.

Chronic amoebic colitis is sometimes difficult to treat and usually more than one drug, given in rotation, is needed to achieve reasonable success. It must be remembered that some of the symptoms of colitis may be due to 'irritable colon' or certain pathological changes which may not regress rapidly, even though the colon is cleared of organisms. Hence, other supportive and symptomatic therapy such as adjustment of the diet and use of antispasmodics may be needed.

Amoebic hepatitis: Emetine hydrochloride, metronidazole and chloroquine diphosphate with or without tetracyclines are effective in this condition. Emetine hydrochloride or dehydroemetine is given deep intramuscularly in the dose of 1 mg. per kg. of body weight for a period of 10 days.

Chloroquine diphosphate, particularly valuable in individuals in whom emetine may be contraindicated, is given in the dose of 500 mg. thrice daily for 2 days followed by 250 mg. twice daily for 2 to 3 weeks. Combined emetine-chloroquine therapy is employed in cases not responding to individual drug alone; however, it must be remembered that both drugs can cause cardiotoxicity and hence, such combination should be avoided, if possible.

Metronidazole (800 mg. three times a day for 5 days) rapidly controls hepatic amoebiasis in majority of cases; the dose of 400 mg. though better tolerated is probably less effective. More prolonged therapy (for 10 days) is likely to be required in patients with a liver abscess. Aspiration and occasionally open surgical drainage are necessary in cases not responding satisfactorily to chemotherapy.

Other forms of extra-intestinal amoebiasis: These respond well to emetine, metronidazole and chloroquine. Aspiration is usually necessary in addition to chemotherapy wherever abscess is present. Open surgical drainage may be required in the case of a secondary infection. Simultaneous administration of tetracycline therapy may be beneficial.

Criteria for cure of amoebiasis: Failure to detect *E. histolytica* in stool specimens obtained at regular intervals for next 2 years is taken as the criterion for cure of amoebic infection. Clinical cure does not signify cure of the disease and relapses can occur.

Prevention: The cysts, responsible for propagation of the disease, are resistant to the agents routinely used to purify water. Chlorine, in the concentration employed to purify water, fails to kill them. It is, therefore, necessary to avoid fecal contamination of water by sanitary disposal of feces. Fly control and detection and treatment of carriers is equally important. The surest way to eliminate cysts from water is to boil it. Prophylactic use of small doses of amoebicides has been tried. Although they have been claimed to be useful, such a procedure will have very limited application, particularly in those areas where possibility of reinfection is always present.

52 Chemotherapy of Other Protozoal Infections

Leishmaniasis is an infection with protozoan organism of the genus *Leishmania.* It exists in three main forms, visceral leishmaniasis or kala-azar, cutaneous leishmaniasis or oriental sore and mucocutaneous leishmaniasis localized largely in South America and hence, termed American leishmaniasis.

VISCERAL LEISHMANIASIS OR KALA-AZAR

This form of the disease, produced by *Leishmania donovani* and transmitted by Phlebotomus sandflies, is characterized by hepatosplenomegaly, irregular fever, anemia, leukopenia and hyperglobulinemia. The disease is endemic in the Mediterranean area, tropical Africa, India, China and South America. In India, it is mostly confined to Assam, Orissa and Bengal.

Life cycle: During its life cycle, the protozoan exists in two forms: the *leishmania forms,* found within the reticuloendothelial cells of the liver, spleen and lymph nodes and within the macrophages of the infected person, and the *leptomonad forms* which develop from the leishmania forms within the digestive tract of the sandfly, after it has fed on the blood of an infected individual. The latter form has a flagella and exhibits motility. The development of the leptomonad forms within the sandfly takes approximately 10 days. These forms are injected by the sandfly into man during its bite. In man, they attack the reticuloendothelial cells and undergo transition into the leishmania forms.

Diagnosis of kala-azar depends upon the demonstration of the leishmania forms in the peripheral blood or in the aspirate obtained by sternal, splenic, liver or lymph node puncture. The last mentioned procedure is safer. Blood culture on NNN medium is a more certain but time-consuming method of diagnosis.

The drugs used in the treatment of visceral leishmaniasis are:

I. Pentavalent antimony compounds: Urea stibamine, Sodium stibogluconate and Ethyl stibamine.

II. Diamidine derivatives: Dihydroxystilbamidine isethionate and Pentamidine isethionate.

I. Pentavalent antimony compounds: The pentavalent antimony compounds exhibit little activity against the leptomonad forms of Leishmania *in vitro.* Their efficacy *in vivo* suggests their possible reduction into trivalent antimony compounds in the body.

(a) UREA STIBAMINE I.P.: It is formed by the interaction of stibanic acid with urea. It is a pale greyish, brownish or pinkish, amorphous, dry powder, readily soluble in cold water. It contains not less than 38 per cent and not more than 42 per cent of antimony. The compound is apt to undergo chemical changes if exposed to air.

Urea stibamine injection I.P. is administered intravenously in the dose of 50 to 200 mg. on every alternate day for about 4 weeks. The total adult dose required to achieve cure is about 3 gm. The drug may be administered intramuscularly to infants in the dose of 10 to 80 mg., the total dose required for cure being 600 to 700 mg.

Urea stibamine is an effective preparation which often succeeds in cases resistant to other antimonials. It is usually given along with sodium stibogluconate in resistant cases. Intermission in treatment leads to development of resistance by the parasites.

(b) SODIUM ANTIMONY GLUCONATE I.P. (Solustibosan, Pentostam): This is a colourless, amorphous powder, extremely soluble in water. It contains not less than 30 per cent and not more than 34 per cent of antimony.

Sodium antimony gluconate injection I.P. contains 2 g. of the drug (600 mg. of antimony) in 6 ml. of water. It is administered by intramuscular or intravenous injection. The initial dose is 6 ml. for sensitivity test, followed by 10 to 15 ml. of the drug daily or on alternate days till a total of 120 ml. is reached for an adult weighing 60 kg. On account of the danger of allergic reactions, a break of 10 days between the 5th and the 6th injection is usually advised, for observation of any adverse symptoms.

(c) ETHYL STIBAMINE: This drug, a complex mixture of para-amino benzene stibonic acid, para-acetyl-aminophenylstibonic acid, antimonic acid and diethylamine, contains 40 to 44 per cent of metallic antimony and is comparatively less toxic. A freshly prepared 25 per cent or 5 per cent solution is administered by intramuscular or intravenous routes respectively. The drug should preferably be given on alternate days. The first adult dose is 100 mg., the second 200 mg., and 300 mg. thereafter. The total curative dose varies from 3 to 4 gm. Similar dose is advocated for patients in relapse.

Adverse reactions to antimony compounds: The detailed toxicity of heavy metals is discussed in Chapter 67. The common adverse effects include a metallic taste in mouth, nausea, vomiting, diarrhoea, giddiness, delirium, a considerable rise or fall in body temperature, muscular pain and jaundice. Hematuria and blood dyscrasias may occur and pre-existing bronchitis or pneumonia may be aggravated. A few cases of anaphylactic shock have also been reported.

II. **Diamidine derivatives:** These drugs are more potent leishmanicidals and also more toxic than the pentavalent antimony compounds. They are usually reserved for cases resistant to antimonial chemotherapy. They are also useful for prophylaxis against *T. gambiense* and in the treatment of early Gambian and Rhodesian trypanosomiasis.

(a) DIHYDROXYSTILBAMIDINE ISETHIONATE: This is administered intravenously in the dose of 250 mg. daily for 10 days. The course may be repeated after an interval of 2 weeks and a total dose of 7.5 gm. should be given over a period of 4 to 5 weeks. If the disease does not respond to one diamidine preparation, another derivative may be tried.

(b) PENTAMIDINE ISETHIONATE (Lomidine): This drug is administered by intramuscular injection in the dose of 180 mg. initially and the dose is then increased gradually to 200 mg. daily for 7 to 10 injections. A second course may be given after an interval of 1 to 2 weeks. The drug, however, appears to the less effective and may sometime cause severe, irreversible hypoglycemia. In resistant cases, the antibiotic amphotericin B may be successful.

Adverse reactions to diamidine derivatives: Headache, fever and rigor are fairly common with these compounds but usually respond to medication with antihistaminic drugs. Intravenous administration of these compounds may result in marked hypotension, severe circulatory collapse, urticaria and angioedema due to histamine release. Peripheral neuropathy and renal and hepatic damage are encountered with stilbamidine.

ORIENTAL SORE

This condition, with a geographical distribution similar to that of kala-azar, is caused by *Leishmania tropica.* The parasite is transmitted by another species of phlebotomus sandfly.

The drugs used in the treatment of this condition include:

(i) SODIUM ANTIMONY GLUCONATE I.P.: Administered intravenously in the dose of 600 mg. daily for 10 days. The drug is particularly useful for treating multiple sores.

(ii) STIBOPHEN (FUADIN) I.P.: A trivalent antimony compound, administered as a 6.4 per cent solution by intramuscular route. Approximately 3 to 5 ml. of the drug are given on every alternate day for 8 to 10 injections.

(iii) MEPACRINE HYDROCHLORIDE 100 mg. dissolved in 2 ml. of distilled water and infiltrated in the lesion is successful in early cases.

(iv) DEHYDROEMETINE RESINATE 3-7 g. daily by mouth for 10 days has given encouraging results.

Sores on the face and hands often get secondarily infected and tend to become chronic. Antibiotic therapy, in addition to intravenous injections of antimony, is required in such cases.

AMERICAN MUCOCUTANEOUS LEISHMANIASIS

This condition, caused by *Leishmania brasiliensis*, is characterised by skin granulomas and ulcerative lesions of the nose, mouth and pharynx. The drugs used in this condition include the pentavalent antimonials, mepacrine and the antibiotic amphotericin B. The last mentioned drug is administered in the dose of 25 mg., dissolved in 500 ml. of 5 per cent dextrose, given over a period of 6 hours every alternate day for a period of 15 days. The dose may be increased subsequently upto 50 to 75 mg..

TRYPANOSOMIASIS

This disease, caused by parasites of the genus *Trypanosoma*, is characterised by irregular and chronic fever, skin eruptions, lymphadenitis, physical and mental lethargy and sometimes death. The disease can be divided into two main forms: African trypanosomiasis or sleeping sickness caused by *Trypanosoma gambiense* and *Trypanosoma rhodesiense* transmitted by tse-tse and open woodland flies respectively; and South American trypanosomiasis caused by *Trypanosoma Cruzi* transmitted by blood-sucking Reduviid bugs.

African trypanosomiasis: The treatment of sleeping sickness should be undertaken in its earlier stage when the parasite has not invaded the central nervous system. The drugs used for treatment are:

(a) SURAMIN SODIUM (Bayer 205): This drug, introduced into therapy in 1940, is a complex organic urea compound, particularly useful in treating the more acute Rhodesian form of African trypanosomiasis. Early infections with *T. gambiense* also respond well to suramin. It is also a useful prophylactic agent but has now been replaced by pentamidine for this purpose. The mechanism of trypanocidal action of the drug is not clear. Parasites treated with the drug lose their infectivity but still survive *in vitro* for over 24 hours after exposure. Significant resistance to the drug *in vivo* has not been reported. In addition to trypanocidal activity, the drug is effective against the adult forms of *Onchocerca volvulus*. Its efficacy against microfilariae, however, is doubtful. Suramin is usually administered by intravenous injection as the drug is not adequately absorbed from the gastrointestinal tract and intramuscular administration is painful and likely to cause local necrosis. The drug gets extensively bound to plasma proteins and may persist in the plasma for as long as 3 months after a single intravenous dose. *It does not cross the blood brain barrier and is, therefore, useless in the encephalitic stage of the disease.* In such cases, the arsenical, melarsoprol, is used. Metabolic degradation in the body appears to be insignificant and the drug is slowly eliminated in urine by glomerular filtration.

Suramin may produce a variety of adverse effects including nausea, vomiting, shock, dermatitis, chills, fever, pruritus paraesthesias, photophobia and sometimes, oss of consciousness. Blood dyscrasias may develop occasionally. The drug is nephrotoxic and may give rise to cylindruria, albuminuria and hematuria. It is contraindicated in renal disease.

Suramin sodium is a white powder, soluble in water. A freshly prepared 10 per cent solution in distilled water is given intravenously at intervals of 5 to 7 days for 5-6 injections. The initial dose is 0.5 gm. followed by 1 gm. in subsequent njections. A child under 3 years is usually given 0.25 g., from 3 to 10 years 0.5 gm. and those above ten years 1 gm. As he drug is nephrotoxic, urine should be xamined before each injection.

(b) PENTAMIDINE ISETHIONATE: This drug has trypanocidal activity and nay serve as a substitute for suramin. It s administered in the dose of 3 to 4 mg. of the base per kg. of body weight, on every alternate day for 10 doses by intravenous injection. A single intramuscular lose of pentamidine (300-400 mg.) once every 6 months has been shown to protect gainst the Gambian but not the Rhodeian disease.

(c) **The organic arsenical compounds** ised in African trypanosomiasis are tryparsamide, Mel B and Mel W. These compounds are more toxic than the agents liscussed previously. They are mainly ised in the treatment of meningo-encehalitic stage of the disease.

(i) TRYPARSAMIDE: This pentavalnt organic arsenical containing 25 per ent of arsenic is administered usually fter a course of suramin. The drug penerates into the C.S.F. Its trypanocidal ctivity is probably due to its conversion nto a trivalent form by the tissues of the ost. The drug is particularly useful in reating the encephalitic stage of *T. ambiense* infection. *T. rhodesiense* is usually resistant to this drug.

Tryparsamide is a highly toxic drug, Apart from dermatitis, mild liver damage and skin rashes, the drug may produce Jarisch-Herxheimer reaction and nitritoid crisis. The most serious toxicity is the visual injury. Acute blindness may develop suddenly, but usually the ocular symptoms appear gradually, preceded by photophobia, lachrymation and ocular pain. These are followed by dimness of vision, 'shimmering' or 'dazzling' and contraction of visual fields. Blindness due to optic atrophy may follow if the drug is not discontinued. Dimercaprol, a specific antagonist of arsenic, is used to treat the toxicity.

Tryparsamide is given intravenously as a freshly prepared 20 per cent solution in distilled water. The first dose of 1 gm. is followed at intervals of 5 to 7 days by 9 to 10 doses, each of 2 g. Children do not tolerate the drug well. The course of the drug may be repeated after an interval of 1 month. As mentioned previously, the drug may be given following suramin therapy but its administration after pentamidine results in severe toxicity.

(ii) MEL B: (Melarsoprol): This trivalent organic arsenical, effective in the early and the late meningoencephalitic stages of trypanosomiasis, is administered intravenously in the dose of 3.6 mg. per kg. (upto a maximum of 200 mg.) dissolved in propylene glycol. The injection is given slowly on alternate days for 3 days. The drug may be repeated after an intermission of 3 weeks in cases with involvement of the central nervous system. The drug has cured many late cases of *T. rhodesiense* infection. Though it is highly toxic it is less so than tryparsamide. The toxic manifestations include vomiting, abdominal colic, neuritis and arsenical encephalopathy. The latter benefits little from dimercaprol and may occasionally result in death.

Mel B is contraindicated in severely debilitated patients and in those with hepatic and/or renal damage.

(iii) MELARSONYL POTASSIUM (Mel W, Trimelarson): This water soluble derivative of Mel B is given as a 5 percent solution by intramuscular injection. The initial dose is 2 mg. per kg.; then 4 mg. per kg. is given daily for 3 days. In severe cases, another course in the dose of 4 mg. per kg. for 4 days may be given after a week. The preparation is probably less toxic but also less effective than the parent compound in advanced T. rhodesiense infection, but may be equally effective in T. gambiense infection. The drug is also useful in onchocerciasis and in guinea worm disease.

(d) NITROFURAZONE: This drug has been recently employed for trypanosomiasis in patients who have relapsed after other treatment. It is given by mouth in doses of 500 mg. 3 times daily for 7 to 10 days. For children, a dose of 30 mg. per kg. is recommended. The adverse manifestations include peripheral neuritis, an impairment of pyruvate metabolism and hemolysis in patients with deficiency of glucose 6-phosphate dehydrogenase.

South American Trypanosomiasis: All the drugs used in African trypanosomiasis have failed to affect this condition. A variety of other drugs, including pyrimethamine, mepacrine, aminopterin, nitrofurans, amphotericin B and puromycin have been given a trial. These may cause a transient disappearance of parasitemia but relapses usually occur. At present, an effective agent for the treatment of this condition is not available.

TRICHOMONIASIS

Trichomonas vaginalis is the infectious protozoon most commonly associated with vulvovaginitis during reproductive years; infection with this agent occurs only infrequently during preadolescence and after the menopause. The primary sign of the infection is a profuse, malodorous, frothy and purulent vaginal discharge (leucorrhoea), greenish yellow in colour. Other symptoms include pruritus, burning, edema, dyspareunia and urinary frequency. Infection in male is often symptomless. The condition is diagnosed by microscopic examination of fresh material from the vagina or of semen, prostatic fluid obtained by massage or urinary sediment. The flagella of the protozoan can be identified in a wet smear.

A variety of agents have been used in the local treatment of trichomoniasis. These are useful when extravaginal sources of reinfection are not present. They include:

(i) halogenated hydroxyquinolines like iodochlorohydroxyquinoline, diiodohydroxyquinoline;

(ii) organic arsenicals like carbarsone and acetarsone and

(iii) agents like furazolidone, surfactants like sodium lauryl sulfate, dioctyl sodium sulfosuccinate, triclobisonium and povidone iodine.

These are discussed elsewhere.

Other local agents like vinegar, boric acid and lactic acid are used to lower the vaginal pH to its usual acidity (3.5 to 4.5). This facilitates the growth of the normal vaginal flora and results in suppression of the trichomonal infection..

They are often combined with deodorizers like thymol, menthol, or eucalyptol.

METRONIDAZOLE (Flagyl, Unimezol, Metrogyl): Metronidazole is a systemic trichomonacide, highly effective by mouth. It acts as a trichomonacide both *in vivo* and *in vitro*. In addition, it is also effective against non-sporing anaerobes (bacteroides fragilis) and against protozoa, *E. histolytica* and *Giardia lamblia*.

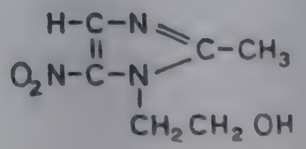


Fig. 52.1: Metronidazole.

Absorption, fate and excretion: Metronidazole is adequately absorbed from the gut but the plasma levels of the drug are low. The drug crosses the placental barrier and is present in milk. It is partly metabolised in the body and after large doses, the metabolites may impart a dark colour to the urine.

Adverse reactions: These, as a rule, are mild and seldom necessitate discontinuation of therapy. Nausea, anorexia, abdominal pain and metallic taste in the mouth are fairly common. Headache, stomatitis, cystitis, dizziness, vertigo, ataxia, urticaria, pruritus and flushing are rarely reported side-effects. The drug may produce an antabuse like reaction characterised by flushing, nausea and vomiting in some patients after ingestion of alcohol.

Chemically, metronidazole contains a nitro group which is associated with the occurrence of blood dyscrasias. Although frank blood dyscrasias with this compound have not been reported, a temporary decrease in total white cell and polymorphonuclear counts has been observed. It is, therefore, necessary not to use the drug indiscriminately. The drug has been shown to possess possible carcinogenic and mutagenic effects in experimental studies.

Preparations and dosage: Metronidazole is available for oral therapy as 200 mg. tablets and as vaginal tablets containing 500 mg. It is also available in suspension form for pediatric use and as rectal suppositories containing 1.0 and 0.5 g. Further, it has also been used intravenously. Orally, the dosage of metronidazole is 600 mg. daily for 10 days. If a concomitant vaginal insert is used, the oral dose in female should be reduced to 500 mg. daily. Such a combined treatment given for 10 days is often useful in refractory cases; a second course can be instituted after 4 to 6 weeks.

Therapeutic uses: (a) *Trichomoniasis*: Vaginal discharge is a common complaint in general practice. It must be emphasized that many discharges are non-infective and hence it is wrong and may even be harmful to use systemic or local antimicrobial drugs unless proper diagnosis is made.

In women of the child-bearing age excessive vaginal discharge (leucorrhoea) may simply be due to pelvic congestion or increased secretion of the cervical glands as in cervical erosion or during oral contraceptive medication. In such cases bacteriological examination is negative and no drugs are indicated. What is needed is reassurance and advice on simple hygiene and cauterization of the cervical erosion, if present.

Vaginal discharge due to infections should be treated according to the causative organism. *Trichomonas vaginalis* is by far the commonest one, followed by *C. albicans*. Typically, trichomoniasis presents as an intense vaginitis with a purulent, offensive discharge. Candidial vaginitis is less intense with thin and 'cheesy' discharge and adherent plaques on the vaginal wall. Sometimes, accurate clinical differentiation between these lesions is difficult.

Trichomoniasis responds well to oral metronidazole 400 mg twice daily for 5-8 days, which is a treatment of choice. A second course may be instituted after 4-6 weeks. Since it is a urogenital infection, simply using local pessaries without systemic therapy is unsatisfactory.

Trichomoniasis is sexually transmissible and it is better to administer a course of metronidazole to the infected male and to male sexual contacts of infected females. It is advisable to avoid sexual intercourse until cure of trichomoniasis has been confirmed. Infections due to *C. albicans* and gonococcal, and puerperal infections need appropriate antibiotic therapy. (See Chapt. 46, 49).

(b) *Giardiasis*: Metronidazole, is given in doses of 200 mg. 3 times daily for 5 days; elimination of giardia should be verified by careful stool examination.

(c) *Ulcerative gingivitis* (Vincent's stomatitis): Usually 3-4 days treatment is necessary.

(d) *Intestinal and hepatic amoebiasis*: Discussed in Chapter 51.

(e) *Bacteroide infections*: Metronidazole is effective in chemoprophylaxis and treatment of infections due to non-sporing anaerobes (bacteroides) and has been used in gynecological and appendicular surgery to reduce post-operative morbidity. For this purpose, metronidazole is given rectally as suppositories in the dose of 1 g. eight hourly until oral feeding begins. It is then administered orally in the dose of 200 mg. three times a day for 7-10 days. In children under 12, the rectal dose is reduced to 0.5 g. eight hourly.

Combination of metronidazole and lincomycin appears to be synergistic and has been used with advantage to treat intra-abdominal sepsis, pelvic infection and anaerobic pulmonary infection.

(f) *Dracunculosis*. (See Chapter 54.)

TINIDAZOLE : This is a newer imidazole derivative, structurally related to metronidazole and has similar therapeutic capabilities. It is claimed to be effective in a single oral dose of 2 g. in the treatment of vaginal trichomoniasis and giardiasis. The drug has also been used in amoebiasis.

GIARDIASIS

Giardia lamblia is a flagellate protozoon parasite of the small intestine. Like E. *histolytica*, it has no animal host and is transmitted from man to man by fecal contamination of food and water. It can cause diarrhoea, anorexia, nausea, vomiting, abdominal pain and weight loss. Both the cysts and the trophozoites may be found in the stools. Giardiasis often exists in association with *E. histolytica* infection and if heavy, may prevent the detection of *E. histolytica* in stools.

Drugs used in giardiasis are mepacrine, diiodohydroxyquinoline, metronidazole, dehydroemetine resinate, 4-aminoquinolines and furoxone. They are discussed in detail elsewhere. Mepacrine is probably the drug of choice.

53

Chemotherapy of Viral Infections

Many bacterial infections can now be successfully controlled by chemotherapeutic agents. Satisfactory treatment of virus infections, however, still remains difficult. Many antiviral drugs found to be effective in laboratory experiments have proved to be disappointing in clinical practice.

Viruses, unlike bacteria, have no cell wall and the enzyme systems associated with it. A virus is made up of a nucleic acid component. Certain other constituents protect this nucleic acid moiety from the action of various body fluid enzymes. Viruses are of two types: (i) those containing deoxyribonucleic acid (DNA) and (ii) those containing ribonucleic acid (RNA). The major difficulties involved in the chemotherapy of viral infections are:

(1) Viruses, unlike bacteria, are intimately parasitic on host cells. They are obligatory intracellular agents. Hence, a drug that is expected to destroy the virus is likely to be toxic to normal host cells.

(2) Certain viruses multiply in the cytoplasm while others do so in the nucleus of the infected cell. A drug which acts on a virus in the cytoplasm may not necessarily act on a virus that multiplies in the nucleus and vice versa.

(3) The severity of infection produced by a virus and its response to a given chemotherapeutic drug differ considerably in different species of animals.

(4) The laboratory screening tests available at present for antiviral compounds are inadequate and difficult. Further, although the antiviral tests *in vitro* measure the ability of a new drug to inhibit the viral growth, they cannot predict its therapeutic efficacy.

(5) Our knowledge of the pathogenesis of viral diseases is still very meagre and in many viral infections, the greater part of the viral multiplication takes place before the clinical diagnosis can be made. The antiviral compounds are likely to be most effective during the stage of multiplication of the virus, which is difficult to detect.

Of the various antiviral compounds studied experimentally, only those which have been shown to be of some benefit in human infections are discussed here. These are:

(a) Compounds interfering with the nucleic acid synthesis, e.g. Idoxuridine.

(b) Thiosemicarbazones e.g. Methisazone (Marboran), M. & B. 7714.

(c) Natural substances e.g. Interferon

(d) Miscellaneous agents e.g. Amantadine, antiviral antibiotics, Gamma globulin.

IDOXURIDINE (5-Iodo-2'-Deoxyuridine): This compound is chemically closely related to thymidine and acts by competing with it in the synthesis of DNA, thereby preventing the utilisation of thymidine. Experimentally, it prevents the replication of DNA-containing viruses such as the herpes and vaccinia viruses. The drug, however, also interferes with the synthesis of normal cellular DNA and, hence, is too toxic for systemic use. It has been mainly employed locally in the treatment of herpetic ulcerations of the cornea. It is generally used as 0.1% drops, applied every 1-2 hours. Frequent recurrence of the original infection is a great disadvantage of this therapy. The drug has been used by intravenous infusion in herpes encephalitis in man with some success. Toxicity includes leucopenia, thrombocytopenia, alopecia and liver damage. Viruses can develop resistance to idoxuridine.

CYTOSINE ARABINOSIDE: This drug

is claimed to be as effective as but less toxic than idoxuridine. It acts like idoxuridine and has been used by rapid intravenous infusion in herpes zoster and simplex infections.

Recently, adenin arabinoside has also been used similarly.

THIOSEMICARBAZONES: The best investigated compound from this group is N-methyl isatin beta-thiosemicarbazone (Methisazone). It is a fine orange powder, almost insoluble in water. This compound is mainly effective against vaccinia and smallpox viruses. Its mode of action is not known.

Methisazone, administered orally in doses of 2-3 g. daily in divided doses, has been shown to reduce the incidence of smallpox in contacts and hence, is of prophylactic value. It is not useful in the treatment of established smallpox. The drug is claimed to be effective in severe vaccinia infections like eczema vaccinatum and vaccinia gangrenosa. It has been used for the prevention of complications of vaccination; the dose used is 100 mg. per kg. as a loading dose, followed by 50 mg. per kg. daily for 3-6 days starting on 4th day of vaccination.

Adverse reactions: These include nausea, vomiting, diarrhoea, blood dyscrasias and liver damage.

M. & B. 7714: This compound resembles methisazone in its action and toxicity.

INTERFERONS: These are a family of natural substances produced by the cell, which protects the cell from a virus without producing toxicity to the host. They can, therefore, be considered as potent, broad spectrum, antiviral compounds with a high therapeutic ratio. They are active against both DNA and RNA viruses.

The chemical structure of interferons is not known. They are proteins of molecular weights beween 19,000 and 160,000 and are relatively species specific and nonantigenic. Interferon prepared in monkey kidney cells is effective in man. Unlike the neutralizing antibody, interferon has no effect on extracellular virus nor does it prevent cell penetration by the virus. It does not inactivate the virus but appears to act very soon after the virus has entered the cell, affecting its replication process. Normally it is produced in the body in response to viral infections. Human placenta or leucocytes are possible rich sources of interferons.

Clinical results with exogenously administered interferons are disappointing. This is probably due to the difficulty in achieving an adequate concentration of interferons at the desired site. The large molecule of interferon penetrates the cell rather slowly. The drug is likely to act more effectively if it reaches the cell before the virus.

Certain substances like the live attenuated measles virus, bacterial endotoxins, other microbial extracts, anionic plastics and anionic polysaccharides can stimulate the production of endogenous interferon. Therapeutic usefulness of such measures is yet to be studied.

Interferon has been used experimentally in the treatment of vaccinia infection in man, with limited success.

AMANTADINE (1-Adamantanamine hydrochloride): This drug has been demonstrated to suppress experimental infection with some strains of influenza virus and rubella virus. It is believed to act by blocking the entry of the adsorbed virus into the cell. It has been shown to be of some use in the prophylaxis and treatment of influenza A in man. Its therapeutic usefulness, however, appears to be limited. Adverse effects is not a major problem though the drug can cause certain psychic and neurological side effects. It is also used in Parkinsonism. (See Chapter 19.)

The drug is administered orally in the dose of 100 mg. once or twice daily.

(+) — CYANIDANOL — 3: This is a flavonoid compound, claimed to decrease the hepatotoxicity of alcohol in laboratory animals. It is reported to decrease serum bilirubin and relieve symptoms such as nausea and anorexia in patients with acute viral hepatitis—B. The mechanism of action is not known but direct effect on hepatitis virus has not been demonstrated. It is given orally. The drug needs further evaluation.

GAMMA GLOBULIN: Roughly, plasma proteins can be fractionated into four important components, namely albumin and the alpha, beta and gamma globulins. The gamma globulin carries antibodies and hence, is also called as 'Human Normal Immunoglobulin' (HNI).

Gamma globulin is synthesized in the cells of the lymphoid system.

The gamma globulin obtained from pooled human, adult blood is known as 'immune serum'. More selective type of gamma globulin against a particular infection can be obtained from the blood of convalescent patients suffering from that disease or from the blood of subjects recently immunised against that disease. The gamma globulin obtained this way is called 'hyperimmune serum' or 'human specific immunoglobulin'.

Gamma globulin can be used both for prophylactic as well as therapeutic purposes. It is administered intramuscularly.

Adverse reactions: Gamma globulin can cause pain at the site of injection. Allergic reactions are known to occur. The drug may give rise to fever, flushing, shivering, joint pain and nausea. Severe bronchospasm, hypotension and collapse, however, are rare and occur mostly following intravenous therapy.

Therapeutic uses:

(a) In patients with *hypogammaglobulinemia:* Normally, the total gamma globulins in the plasma vary between 600 and 1500 mg. per 100 ml. Total serum gamma globulins in normal Indians are much higher than those in Western people. Patients with serum gamma globulins concentration of 200 mg. or less are considered to be definitely suffering from hypogammaglobulinemia. HNI is usually given in dose of 0.025 to 0.05 g. per kg. body weight, at weekly intervals. Usually, very prolonged therapy is necessary along with prophylactic antibiotics against infections.

(b) For giving passive immunity as a temporary protection and in therapy of certain viral diseases:

(i) *Measles and rubella prophylaxis:* HNI will attenuate or prevent the symptoms of measles if given early in the incubation period. The doses recommended are: for attenuation, 250 mg. at all ages; for prevention 250 mg. below one year, 500 mg. at 1-2 years and 750 mg. at 3 years and above. The effect lasts only for a few weeks. In pregnant women exposed to rubella, the dose recommended is 750 mg.

(ii) *Infective hepatitis:* Gamma globulin can suppress the clinical symptoms and if they occur, they are usually mild. The dose of HNI recommended is 750 mg. given prophylactically in contacts. The effect lasts for 6 months. It is not effective in preventing serum hepatitis.

(iii) *Smallpox and vaccinia:* It has been used prophylactically in contacts with a high risk of smallpox e.g. pregnant women, unvaccinated babies. It can also be used to treat complications following vaccination. Usually, hyperimmune serum is preferred in the dose of 0.65 to 1.0 ml. per kg. of body weight, repeated if necessary at weekly intervals.

(iv) *Mumps and poliomyelitis*: Immune gamma globulin has been claimed to be useful in preventing the complications of mumps and in reducing the incidence of paralytic poliomyelitis.

(v) *Tetanus and diphtheria:* Hyperimmune serum specific against these diseases can be used both prophylactically and therapeutically. The details are discussed elsewhere.

(vi) *Miscellaneous:* Occasionally, gamma globulin may be given for preventing secondary infection in susceptible individuals e.g. after burns. This, however, is not routinely recommended.

54 Chemotherapy of Helminthiasis

Worm infestation is one of the major global public health problems more so in tropical countries. Besides the environmental conditions peculiar to tropics, poverty, illiteracy, lack of adequate sanitary facilities and of pure water supply make total eradication of this problem very difficult. Although no definite statistics are available, the number of people suffering from worm infestation in developing countries runs into millions. The commonest parasites observed in India are roundworms, hookworms, threadworms, tapeworms, guinea worms and filarial worms.

Worms can cause various gastrointestinal and general symptoms. In addition, some of them can cause blood loss, nutritional deficiencies, urticaria and other allergic manifestations and even intestinal obstruction. A careful examination of stools may often spare the unnecessary removal of teeth and tonsils, usually blamed for 'septic foci', in cases with 'resistant urticaria'.

The helminths are multicellular organisms possessing three germ layers and exhibiting a bilateral symmetry. They are classified into two major phyla: phylum platyhelminthes and phylum nemathelminthes (Table 54.1). *Anthelmintics* are drugs used in the treatment of helminthiasis.

Experimentally, anthelmintic drugs can be studied *in vivo*, in experimental worm infestations produced in animals and in patients. The *in vitro* testing is usually done on a helminth like the roundworm, mounted in an isolated organ bath. The significance of such work, however, is limited as the environment in which the parasite exists inside the host body can hardly be reproduced under the conditions of such experiments. Various techniques for testing the anthelmintic agents in experimental animal helminthiasis have been

Table 54.1: **Helminths**

Phylum Platyhelminthes

Cestodes

TSBT *Taenia saginata* (Beef tapeworm)
TSPT *Taenia solium* (Pork tapeworm)
Diphyllobothrium latum (Fish tapeworm)
Echinococcus granulosus (Dog tapeworm)
Hymenolepis nana (Dwarf tapeworm)

Trematodes

Schistosomes: *S. haematobium. S. mansoni* and *S. japonicum.*
Flukes: *Fasciola hepatica* (Liver fluke), *Fasciolopis Buski* (Giant intestinal fluke), *Clonorchis sinensis* and *Paragonimus westermani*

Phylum Nemathelminthes

Nematodes

I. *Intestinal*
Ascaris lumbricoides (roundworm)
Ancylostoma duodenale and *Necator americanus* (hookworm)
Enterobius vermicularis (thread worm or pinworm)
Trichuris trichiura (whipworm)
Strongyloides stercoralis
Trichinella spiralis

II. *Somatic*
Wuchereria bancrofti (filarial worm),
Onchocerca volvulus,
Dracunculus medinensis (guinea worm)
Loa loa

evolved. Thus, a prospective anthelmintic agent is first studied in various experimental worm infestations in animals like mouse, rat, cat, dog and pig before it is tried in man.

For a clinical trial of a potential anthelmintic agent, a well established anthelmintic drug with a similar spectrum should always be incorporated in the experimental design so as to ensure an effective comparison. The efficacy of the new drug can be gauged by counting the ova or eggs present in the stools. Efficacy of a drug against taeniasis, however, can only be judged by the appearance of the scolex in the stools. Patients suffering from multiple parasitic infestations are ideal for investigating a new anthelmintic drug claimed to have a broad spectrum of action. Such patients, however, are not suitable for evaluating a new anthelmintic drug with a narrow spectrum of action.

An ideal anthelmintic should have a broad spectrum of action and it should achieve a high percentage of cure, preferably with a single therapeutic dose. Purgation before and following the anthelmintic should not be necessary; it should not get absorbed, be palatable, cheap and free from toxic manifestations.

An anthelmintic drug which kills the worm is called *vermicidal,* while that which affects the worm in such a way that it is easily expelled is called as a *vermifuge.*

In recent years, many anthelmintics with selective actions and low toxicity, relatively safe even in the undernourished individuals, have been introduced. They are convenient to administer as no prior preparation is necessary and no follow up purgation is required unless constipation is present.

In endemic areas, the main aim of anthelmintic treatment should be to reduce the load of infection below the level of

Table 54.2: Common forms of Helminthiasis and the Drugs used in their Treatment

Infestation	Drug of choice	Other drugs used
Taeniasis	Mepacrine Niclosamide	Chloroquine, paromomycin, Dichlorophen
D. latum	Niclosamide	Mepacrine, Paromomycin, Dichlorophen
H. nana	Paromomycin	Niclosamide, Mepacrine, Dichlorophen
Ascariasis	Piperazine Tetramisole	Pyrantel, Bephenium, Mebendazole
Ancylostomiasis	Tetrachlorethylene Bephenium	Mebendazole, Pyrantel, Tetramisole, Bitoscanate
Oxyuriasis	Viprinium	Mebendazole, Pyrantel, Piperazine
Trichuriasis	Mebendazole	Thiabendazole, Bephenium
Schistosomiasis	Lucanthone	Trivalent antimonials, Amphotalide, Niridazole
Filariasis	Diethylcarbamazine	Carbarsone
Dracontiasis	Metronidazole Niridazole	Thiabendazole
Strongyloidiasis	Thiabendazole	Mebendazole

clinical significance. Complete parasitological cure is unnecessary and often not possible. In achieving this, safety and economic considerations must determine the choice of the drugs in mass therapy.

The anthelmintic drugs available for therapy are listed in Table No. 54.2.

DRUG THERAPY OF TAPEWORMS

This infestation is transmitted by ingestion of infected beef or pork and can be prevented by avoiding the ingestion of suspected meat or by its thorough cooking. The drugs used in taeniasis are:

MEPACRINE: This is the most useful drug in the treatment of taeniasis. In addition to its efficacy in *T. saginata* and *T. solium* infestations, the drug is useful against *H. nana* and *D. latum*. The mechanism of the anthelmintic effect of mepacrine is not understood but it acts as a vermifuge. Its other pharmacological actions and toxicity are discussed in Chapter 50.

The major drawback of mepacrine as an anthelmintic is its liability to cause nausea and severe vomiting, when given in an effective dose by mouth. These can be minimised by administration of an antiemetic agent before mepacrine, by giving the anthelmintic with sodium bicarbonate to reduce the gastrointestinal irritation, and by confining the patient to bed during drug therapy.

The anthelmintic dose of mepacrine hydrochloride is 1 g. Before therapy, the patient should be placed on a bland, low residue, semisolid diet for 2-3 days. A saline purgative, magnesium sulfate 15 g. may be administered the night before but is not mandatory. The next morning, the patient is given an antiemetic (chlorpromazine 25 to 50 mg.) on empty stomach, followed 2 hours later by mepacrine 1 g., given in 3 divided doses at 30 minute intervals, along with sodium bicarbonate 600 mg. with each dose. The patient is asked to lie down in bed and frequent sips of water are advised to facilitate the passage of the drug into the jejunum. A saline purge is given after 1 to 1½ hours. The stools should be carefully collected, sieved and examined for the scolex. This treatment may be repeated after 1 to 2 weeks.

Mepacrine can also be administered by a duodenal tube in the dose of 800 mg., dissolved in 100 ml. of water.

CHLOROQUINE: This drug, given in a single total dose of 2 g. in the morning, on an empty stomach, followed later by a saline purgative, achieves a fair rate of cure in taeniasis. It is, however, more effective against fish tapeworm than pork and beef tapeworms. It also can cause severe nausea and vomiting.

Camoquin given as a single dose, 0.6 to 0.8 g (3-4 tablets), repeated after 6 weeks, is also claimed to be effective.

NICLOSAMIDE (Chlorsalicylamide, Niclosan): This drug is effective in *T. saginata, T. solium* and *H. nana* infestations. Its efficacy against *D. latum,* however, is not established.

Niclosamide is a vermicidal drug. Unlike mepacrine, the segments of the worm which are voided after chlorsalicylamide therapy are partially digested by the action of the proteolytic enzymes of the small intestine and this makes identification of the scolex impossible. The criterion for cure with this drug, therefore, is absence of eggs and proglottids in the stools for 3 to 4 months after therapy. This is the period required for *T. saginata* to mature and shed mature proglottids from the scolex. However, identification of scolex is important when treating *T. solium* infestation, as cysticercosis i.e. harbouring of the larval forms (cysticerci) in the tissues of the host may develop if the infestation is not completely eradicated. This makes it mandatory to use a purge within 1-2 hours after the drug is given, in order to prevent digestion of the segments. Alternatively, mepacrine may be used for treating *T. solium* infestation.

The major advantage of chlorsalicylamide is its lack of toxicity as the absorption of the drug is negligible. It is a yellow, white powder, almost insoluble in water, available as 500 mg. tablets.

In the treatment of taeniasis, after keeping the patient on a low residue diet on the day before and fasting overnight, 2 tablets of the drug (1 g.) are given in the morning on an empty stomach. The tablets should be chewed and not swallowed in order to ensure a thorough mixing of the drug with the intestinal contents. Another 1 g. is given after 1 hour. A saline purge may be given 1½ to 2 hours after the second dose but is not essential. The recommended dosage in children is 1 g. for those between 2 to 8 years and 0.5 g. in children under 2 years.

Infection with *H. nana* requires prolonged treatment.

PAROMOMYCIN : This antibiotic has been discussed in Chapters 42 and 51. Given orally in the dose of 1 g every 4 hours for 4 doses, it is also effective against *T. saginata, T. solium, D. latum* and *H. nana.*

DICHLOROPHEN : This drug, used extensively in veterinary medicine, has also been found useful in human *T. saginata* and *T. solium* infestations. The drug directly kills the parasites and the partially autolysed products are eliminated in feces. This makes identification of the scolex difficult. The criterion of cure, therefore, is similar to that adapted for chlorsalicylamide therapy. The drug has also been claimed to be effective in *D. latum* and *H. nana* infestations.

Adverse effects include gastrointestinal disturbances leading to nausea, vomiting, diarrhoea and abdominal colic. Urticaria occurs in a small number of patients. Jaundice and even death have followed very large doses.

Dichlorophen is a white or slightly cream-coloured powder, with phenolic taste and is almost insoluble in water. It is available as tablets containing 500 mg. of the drug.

The adult dose of the drug is 6 g. and for children, 2 to 4 g. on each of 2 successive days. There is no need for preliminary fasting. An after-purge may be given in case of T. solium.

Dichlorophen is contraindicated in the presence of liver disease.

MALE FERN (Aspidium oleoresin): Male fern, probably the oldest remedy in the treatment of taeniasis, has lost much of its utility because of its high toxicity and the availability of better therapeutic agents. It was used as the liquid extract (filix-mas). For details, see the previous editions of this book.

DRUG THERAPY OF ROUNDWORMS

PIPERAZINE : Piperazine salts, tried initially without success in the treatment of gout because of their ability to dissolve uric acid crystals *in vitro*, turned out to be potent anthelmintics and now constitute the mainstay of the therapy of ascariasis and oxyuriasis.

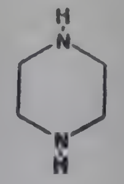


Fig. 54.1: Piperazine.

Piperazine probably owes its anthelmintic activity to its ability to produce flaccid paralysis of the muscles of the parasites. Such narcotised parasites can then be easily expelled by peristaltic movements. Experimental studies indicate that the drug reduces the formation of succinate in the round worm, a substrate necessary for supplying energy for the muscular contraction of the worm. In *in vitro* studies, piperazine blocks the acetylcholine produced contraction of the ascaris muscle. This blocking effect is competitive in nature. The parasites expelled as a result of drug action are paralysed but not dead. This eliminates the danger of worm migration and absorption of the autolysis products of parasites. Apart from the anthelmintic action, the drug does not show any other significant pharmacological activity in the human host.

Absorption, fate and excretion: Piperazine is readily absorbed from the gut, to the extent of about 30%. The drug is partly metabolised in the body and partly excreted unchanged in the urine. The metabolic fate of the various piperazine salts appears to be similar. However individuals vary widely in their rate of urinary elimination of piperazine.

Adverse reactions: Piperazine has a wide margin of safety. Adverse effects are rare, and usually due to cumulation after large doses. They include nausea, vomiting, diarrhoea and urticaria. Neurotoxic effects have been observed rarely; they include vertigo, muscular incoordination, hypotonia, ataxia of cerebellar type ('worm—wobble') paraesthesiae, blurring of vision and very rarely convulsions. The adverse effects disappear rapidly after discontinuation of the treatment.

Preparations and dosage: A variety of piperazine salts are available for therapy. There is little to choose from among the various preparations except for the cost.

(i) Piperazine citrate I.P. is a white, crystalline powder, acidic in taste and freely soluble in water. It is available as 300 mg. tablets (equivalent to about 250 mg. of piperazine hydrate), as an elixir containing 18 g. of the salt in 100 ml. of water and as a mixture for infants containing 720 mg. of the drug per 5 ml..

For ascariasis in adults, a single dose of 5 g. is administered. Alternatively, 3 to 3.5 g. of the drug may be given daily for 2 consecutive days. The equivalent dose of the elixir is upto 30 ml. Children are given the drug in the dose of 75 mg. per kg. (5 to 7 ml. of the 'mixture for infants' per year of age to a maximum of 30 ml.) in a single dose. Preliminary fasting is not necessary. The drug is preferably administered in the evening and a saline purge may be given on the next morning to facilitate the expulsion of parasites. A purge, however, is not obligatory.

(ii) Piperazine hydrate: The doses of piperazine salts are usually expressed in terms of this salt. Dose: Adults, 4 g. in a single dose. Children, 120 mg. per kg. upto a total dose of 4 g.

(iii) The other salts used are adipate, phosphate and calcium edetate. The dose is customarily expressed in terms of the hydrate equivalent. Thus, 100 mg. of piperazine hydrate is equivalent to 120 mg. of adipate, 104 mg. of phosphate and 214 mg. of calcium edetate.

The application of piperazine in oxyuriasis is discussed elsewhere.

PYRANTEL PALMOATE: This drug is highly effective against roundworms and *E. vermicularis* and a little less effective against hookworms. In contrast to piperazine, it has a depolarizing, neuromuscular blocking action and causes spastic paralysis of the worms. In ascariasis and enterobiasis, it is usually given in a single dose (10 mg/kg); for hookworm infestation, the same dose is repeated on three successive days. It is not much absorbed from the gut. Adverse reactions are anorexia, nausea, vomiting, diarrhoea, abdominal pain, headache, drowsiness, skin rashes, and raised plasma S.G.O.T. levels. It is available as a suspension containing 250 mg. per 5 ml.

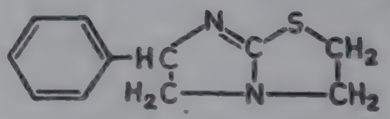


Fig. 54.2: Tetramisole

TETRAMISOLE (Decaris, Levamisole): This anthelmintic is available as white crystalline, water soluble hydrochloride of 2, 3, 5, 6-tetrahydro-6 phenyl-imidazo (2, 1-b) thiazole. In ascariasis, it is effective in the dose of 2.5-5.0 mg./kg., given as a single oral dose. No purgative is necessary. Like pyrantel, it causes a sustained contracture of the somatic muscles of the worm resulting into paralysis of the worm. It also inhibits the production of succinate. Unlike piperazine, tetramisole blocks the acetylcholine response in the nerve muscle preparation of human ascaris, non-competitively. This action is irreversible and appears to be a depolarizing type of neuromuscular block. It is partly absorbed when given orally and excreted in urine within 6 to 10 hours. The adverse effects reported include nausea, vomiting, abdominal pain, diarrhoea, giddiness and drowsiness. It is also effective against hookworms though to a smaller extent.

1-Tetramisole is available as a single dose tablet containing 150 mg. for adults and 50 mg. for children.

Tetramisole has also been shown to have immuno-stimulant properties (see Chapt. 70).

BEPHENIUM HYDROXYNAPHTHOATE (Alcopar): This drug, given in a single dose, is effective in removing roundworms and hookworms of the species *Ancylostoma duodenale*. It is less effective against *Necator americanus*.

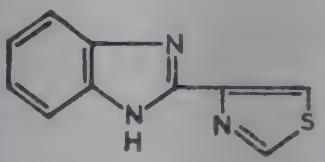
The drug has a moderate effect against whipworms and *Trichostrongylus orientalis*.

Bephenium hydroxynaphthoate is a quaternary ammonium compound which probably acts by producing a contracture of the parasite muscles. This leads to expulsion of the parasites by the peristaltic movements.

The adverse effects reported are nausea, vomiting and diarrhoea. These are probably due to the bitter taste of the drug. In children, it should be given with strong sugar solution. The drug can be administered with impunity in anemic or elderly patients and in pregnant women.

Bephenium hydroxynaphthoate is a yellow, odourless, crystalline powder insoluble in water. It is very bitter. Bephenium hydroxynaphthoate granules N.F. are available for therapy. The adult dose of the drug is 5 g. by mouth (equivalent to 2.5 g. of the base) administered on an empty stomach. Food is not allowed for at least 2 hours after the drug. Children under 20 kg. are given half the adult dose. Purgation is not necessary before or after the drug. Though this dose is effective in eradicating *A. lumbricoides* and *A. duodenale* infestations in majority of cases, for patients of ancylostomiasis with diarrhoea, daily treatment for 3 to 4 days is necessary to ensure complete eradication of the infestation. Bephenium, 50 mg. of the base per kg., with tetrachloroethylene 0.1 ml. per kg., is advocated in mixed infestation with *A. duodenale* and *N. americanus*. The drug is particularly useful in treating coexisting *A. lumbricoides* and *A. duodenale* infestations.

THIABENDAZOLE (Mintezol): This drug, a benzimidazole derivative, has been found effective against roundworms, hookworms, threadworms and strongyloid worms. It is of value in trichiniasis and dracontiasis and is moderately effective in trichuriasis. The drug probably acts by interference with a metabolic pathway essential to a variety of helminths.



(a) Thiabendazole.

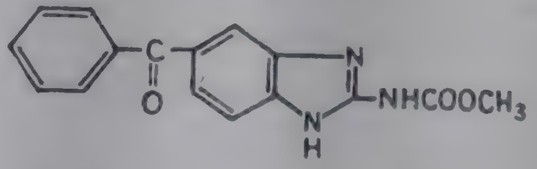


Fig. 54.3: (b) Mebendazol.

Thiabendazole is partly absorbed after oral administration. Approximately 95 per cent of the drug is metabolised and excreted by the kidney as the hydroxylated derivative.

Adverse effects with thiabendazole occur in 15 to 30 per cent of patients. They include allergic reactions, anorexia, nausea, vomiting, epigastric distress, dizziness and fever. These could be quite incapacitating for several hours in some patients. Other adverse effects are pruritus, skin rashes, drowsiness, hypoglycemia and disturbances of colour vision. Blood pressure may fall and liver damage and crystalluria have also been reported.

Thiabendazole is a white, crystalline tasteless compound, slightly soluble in water. The usual dosage in ascariasis and ancylostomiasis is 25 mg. per kg. after the evening meal and repeated after the breakfast for 3 consecutive days. In threadworm infestation, a dose of 25 mg. per kg., evening and morning, repeated after 7 days has given good results. In majority of cases with strongyloid infestation, 50 mg. per kg. in adults and 30 mg. per kg. in children in 2 divided doses at 12 hourly intervals is highly effective. For trichiniasis, 25 mg. of the drug per kg. given twice daily for 5 to 7 days have been reported to cause a symptomatic improvement. The drug is available in chewable tablets of 500 mg. and in an emulsion containing 200 mg. per ml. The drug may be of use in multiple worm infestations.

MEBENDAZOLE (Pantelmin): This is a broad spectrum benzimidazole derivative anthelmentic. Given orally it is not much absorbed. It is effective in ascariasis, enterobiasis, trichuriasis and in hookworm infestation. It also has some action against *S. stercoralis* and the tapeworm. The drug is slow-acting and it may take 2-3 days for parasitic clearance from the gut. It also adversely affects the ova of the trichuris and the hookworm. Adverse reactions are usually mild and consist of abdominal pain, nausea and diarrhoea. It is usually administered in the dose of 100 mg twice daily for 3 days. A single dose of 100 mg repeated after one week is effective in enterobiasis. Mebendazole is probably the drug of choice in the treatment of trichuriasis. The drug is quite expensive at present and should be used in selected cases.

DIETHYLCARBAMAZINE : Discussed later.

Other drugs: Santonin and dithiazamine iodide are no longer recommended because of the availability of safer agents.

DRUG THERAPY OF HOOKWORMS

A. duodenale infestation is extremely common in tropical countries and represents an important cause of iron deficiency anemia. The infestation often exists along with ascariasis. In such a situation, it is preferable to treat ascariasis first, as drugs used solely against ancylostomiasis may irritate the round worms causing their migration or their aggregation into ball-like masses. The former may lead to invasion of the bile duct and the liver, while the latter may precipitate acute appendicular or intestinal obstruction and rarely, perforation. Alternatively, drugs effective against both roundworms and hookworms may be employed.

Drugs used in ancylostomiasis are:

TETRACHLOROETHYLENE (Tetracap): This halogenated hydrocarbon anthelmintic has replaced carbon tetrachloride in the treatment of ancylostomiasis because of the marked hepatotoxicity of the latter. Tetrachloroethylene is more effective against *N. americanus*. It probably acts by producing a reversible paralysis of hookworms which are excreted alive in the feces. Purgation facilitates the expulsion of the paralysed worms but is not mandatory.

Tetrachloroethylene is not absorbed to a significant extent from the gastrointestinal tract. It is an irritant and causes nausea and vomiting. Fat, however, enhances the systemic absorption of the drug and this may lead to giddiness and vertigo. Rarely, loss of consciousness may occur. Severely anemic patients may collapse during tetrachloroethylene therapy. It is advisable, therefore, to treat the severe anemia first and the worm infestation later. The danger can also be minimised by omitting the post-treatment purgation. Rarely the drug can cause jaundice. It should be avoided in patients with liver disease and in very ill children.

Because of its irritant effect on roundworms, tetrachloroethylene is contraindicated in ascariasis mixed with ancylostomiasis. In such cases, ascariasis is treated first, followed by tetrachloroethylene. Alternatively, bephenium hydroxynaphthoate, effective against both the worms, may be employed.

Tetrachloroethylene I.P. is a clear, colourless liquid, having a characteristic, ethereal odour. It is noninflammable and insoluble in water. The drug deteriorates in warm climate and must be stored in a dark bottle in a cool place. For ancylostomiasis, tetrachloroethylene is usually given in the form of gelatin capsules containing 1 ml. of the drug. It may also be given by a duodenal tube or as a mixture containing 0.5 ml. of the drug in 30 ml. of chloroform water. The patient should be advised to take a high protein, high carbohydrate and low fat diet prior to treatment and only a light evening meal should be allowed on the night preceding medication. In the morning, tetrachloroethylene should be ingested on an empty stomach. The usual adult dose of the drug is 3 ml. and for children 0.2 ml. for each year of age upto 15 years. A dose of saline purgative may be administered 2 hours after the drug. During treatment, it is advisable to keep the patient in bed, plenty of milk should be given but other food or alcohol should be avoided. The therapy, if necessary, may be repeated after 10 days.

BITOSCANATE (Jonit) : This anthelmintic, claimed to be equally effective against *A. duodenale* and *N. americanus*, is administered orally in the dose of 200 mg in two divided doses on the first day and 100 mg (single dose) on the second day. Smaller doses are used in children. It causes nausea, vomiting and dizziness. It is available as 100 mg and 50 mg capsules.

Other drugs: Other drugs used in ancylostomiasis are Bephenium hydroxynaphthoate, Thiabendazole, Mebendazole and Pyrantel. It should be noted that no single drug is able to eradicate all the hookworms in 100 per cent cases, and it is necessary to repeat the same or give another drug after appropriate interval.

Adjuvant treatment: This includes administration of iron salts for the correction of anemia. It has been demonstrated that regular, oral administration of 5-10 mg. of elemental iron daily can correct the anemia and raise the hemoglobin levels to 12 g./100 ml. even without immediate treatment of worms. Provision of footwear to avoid larval penetration should be encouraged in endemic areas.

DRUG THERAPY OF THREADWORMS

E. vermicularis is a common parasite found in the caecum and the vermiform appendix. The infestation is more common among the children. The gravid female worm deposits eggs on the perianal skin leading to intense itching. Scratching of this region may lead to autoinfection by ingestion of ova carried under the nails. To prevent this phenomenon, patients should be advised to trim the nails and wash the hands thoroughly before the meals. Symptomatically, an antihistaminic cream applied around the anus relieves itching. Infection can also occur through underclothing, bed linen, lavatory contamination and water contamination. Besides the drug therapy, additional measures are desirable in resistant cases. At night, the patient should wear pants under the pyjamas and gloves which can be boiled. Hands should be washed repeatedly and it may be necessary to treat the whole family simultaneously. Infection can also be disseminated by inhalation or ingestion of dust.

The drugs used in the treatment of threadworm infestation are:

VIPRYNIUM or PYRVINIUM (Vanquin): This drug, a salt of a cyanine dye, is effective against *E. vermicularis* and to some extent in strongyloidiasis. It probably acts by inhibiting cellular oxidation within the worms. The drug is not much absorbed from the gut. The side effects reported are mild and include nausea, vomiting and transient photosensitization. The drug colours the stools red. Viprynium embonate is a deep orange, crystalline powder, almost insoluble in water. The drug is administered by mouth in a single dose of 7.5 mg. (equivalent to 5 mg. of the base) per kg. of the body weight for the treatment of oxyuriasis. One or two subsequent doses at intervals of 2 to 3 weeks may sometimes be necessary. In strongyloidiasis, a dose of 5 mg. of the base per kg. is advocated for 7 days.

PIPERAZINE: The pharmacology of this agent is already discussed. For oxyuriasis, the adult dose is 1 g. of the hydrate twice daily for 7 days. Children between 7 and 12 years should receive the equivalent of 500 mg. thrice daily, those between 4 and 6 years, 500 mg. twice daily and those between 2 and 3 years, 250 mg. thrice daily. Infants between 9 and 24 months may be treated with the equivalent of 250 mg. twice daily. Prior fasting or post-treatment purgation may be used but are not necessary.

Piperazine or viprynium may be repeated two to three weeks after the first dose as the life cycle of the threadworm is about this duration.

TETRACYCLINES: Oxytetracycline, given in the dose of 1 to 2 g. daily for 8 to 15 days cures the majority of cases of oxyuriasis. The high cost and the side-effects of such a therapy, however, mitigate its use.

GENTIAN VIOLET: This drug, formerly used in oxyuriasis, is now superseded by more effective chemotherapeutic agents. It may still be used in strongyloidiasis in the dose of 60 mg. daily by mouth for 16 days. Dithiazanine, however, is superior for this purpose.

Other drugs mebendazole, thiabendazole and pyrantel used in oxyuriasis are discussed earlier.

DRUG THERAPY OF SCHISTOSOMIASIS

Unlike the other infestations discussed so far, schistosomal infestations can be considered as systemic, as the parasites are localised in organs other than the gastrointestinal tract. Man and domestic animals act as hosts for schistosomes, the ova of which contaminate water. Hatched miracidia invade the water snail (intermediate host). Free living cercariae, emerging from the snail, penetrate the human skin and mature into the adult worms. Drugs used in schistosomiasis are:

LUCANTHONE (Miracil D): This drug, primarily effective against *S. mansoni* and *S. haematobium*, probably acts by interfering with the production of eggs by the parasites and eventually leads to death of the adult forms. The drug has no action against *S. japonicum*. It is readily absorbed on oral administration and the major portion is metabolised in the liver. Only about 8 to 10 per cent of the drug is excreted unchanged in the urine. Administration of the drug at 12 hourly intervals achieves a fairly constant therapeutic blood level.

The major drawback of the drug is its high toxicity. Nausea, vomiting, anorexia, dizziness, depression, anxiety and epigastric or abdominal pain are the most common side effects. People with dark skins tolerate the drug much better than those with lighter skins. The drug may cause reversible yellow discolouration of the skin and sclera. Hepatic and renal damage may rarely occur. Hence, the drug should be used with caution in the presence of hepatic and/or renal impairment.

Lucanthone hydrochloride B.P. is available as tablets containing 250 mg. of the drug. The usual dosage for an adult is 1 g. orally, thrice daily, for 3 days, followed by a similar course 1 month later. The total amount of lucanthone hydrochloride given in one course of treatment must be at least 75 mg. per kg. of body weight.

HYCANTHONE: This drug, a metabolite of lucanthone, is claimed to be more effective and less toxic, particularly for *S. mansoni* infestation. It is administered orally in the dose of 4 mg./kg daily for 4 days, or as the sulfamate or methanesulfonate salt intramuscularly, in a single dose of 2-3 mg. base/kg. body weight. The adverse effects reported include gastrointestinal disturbances, loss of body weight, and occasionally jaundice in those with hepatosplenic form of schistosomiasis. These are usually dose-related.

The drug has been shown to be mutagenic *in vitro* and should be avoided in pregnant women and in children below 3 years of age.

TRIVALENT ANTIMONY COMPOUNDS: The general pharmacology of antimony compounds is discussed elsewhere. These drugs destroy the larvae inside the ova. The compounds used in schistosomiasis are:

(i) Antimony dimercaprosuccinate (Stibocaptate) is particularly effective against *S. haematobium*. Dose: 30 to 50 mg. per kg. body weight upto a maximum of 2.5 g. in 5 divided doses by intramuscular injection, at weekly or twice weekly intervals.

(ii) Antimony sodium tartrate is effective against all the three species of schistosomes. Dose: initially 30 mg. daily by intravenous injection. It is then gradually increased by 30 mg. every 48 hours to a maximum single dose of 120 mg. until the total quantity administered is not less than 1.5 g. A 2% solution is usually employed for intravenous injection.

The drug was formerly used in leishmaniasis and in lymphogranuloma inguinale but is now obsolete because of the availability of other safer drugs.

(iii) Antimony potassium tartrate (tartar emetic) is more toxic than the sodium salt. Indications and dosage are similar to antimony sodium tartrate.

(iv) Antimony lithium thiomalate is used as a 6 per cent solution. Dose: 0.5 to 5 ml. intramuscularly, at intervals of 2 to 3 days.

(v) Sodium antimonyl gluconate is used as a 5 per cent solution, given intravenously. Dose 2.5 to 3.3 mg. per kg. daily for 6 to 12 days.

(vi) Stibophen is used as injection containing 6.4 per cent w/v of the drug. The drug is less toxic than antimony sodium tartrate and is particularly useful in *S. mansoni* and *haematobium* infestation. Dose: 1.5 ml. on the first day intramuscularly, 3.5 ml. on the second day, 5 ml. on the third day and every alternate day thereafter to a total of 75 ml.

The antimony compounds, in general, are toxic and may give rise to cumulative toxicity. They should preferably be administered in hospitalized patients and should be avoided in the presence of hepatic and/or renal damage.

AMPHOTALIDE: This recently synthesized compound, administered orally in the dose of 400 mg. per kg. of body weight in divided doses over a period of 5 to 15 days, has been found effective in *S. haematobium* infestation. The side effects reported include nausea, vomiting, abdominal discomfort, loin pains and strangury. The drug is still under evaluation.

NIRIDAZOLE (Ambilhar) : This drug administered in the dose of 25 mg. per kg. per day, orally, for 7 days, has been found to be effective particularly in *S. japonicum* and *S. mansoni* infestations. It is also effective in guinea worm infestation, when used in the same dosage for a period of 10 days. Though effective in amoebiasis, it is rarely used in this condition because of its toxicity which is discussed in Chapter 51.

METRIFONATE (Trichlorophone, Diptirex): This organophosphorus insecticide, given orally in the dose of 5-7.5 mg./kg. daily, for 10-12 days, is claimed to be highly effective in *S. haematobium* infections. It is also effective against ascaris, hookworms and whipworms.

DICHLOROVOS: This is another

organophosphorus insecticide, available in granular resin form that permits its slow liberation in the gastrointestinal tract.

Dichlorovos is effective against trichuris, hookworms, roundworms and schistosomes. Administered orally in the dose of 12 mg./kg. as a single dose, in the morning, preceded by a fast for 12 hours and no food for 2 hours following administration, it has been shown to be highly effective against trichuriasis, and is superior to dithiazanine for this purpose. The drug may produce a transient lowering of plasma cholinesterase, but no significant toxicity has been encountered so far. The drug is still under evaluation.

Drug Therapy of Filariasis

Filariasis is transmitted by the infected Culex mosquito. Although the arsenical and the antimony compounds are claimed to be effective in this condition, the only reliable drug available for prevention and cure of this condition is diethylcarbamazine.

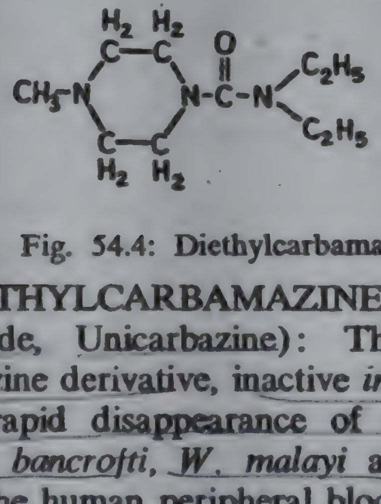


Fig. 54.4: Diethylcarbamazine.

DIETHYLCARBAMAZINE (Hetrazan, Banocide, Unicarbazine): This drug, a piperazine derivative, inactive *in vitro*, leads to a rapid disappearance of microfilariae of *W. bancrofti*, *W. malayi* and *Loa loa* from the human peripheral blood. The drug probably acts by sensitizing the microfilariae so that they become susceptible to phagocytosis and are trapped by the fixed reticuloendothelial cells in the liver sinusoids. The microfilariae of *W. bancrofti* in a hydrocoele, however, are not affected. The drug kills the adult worms of *W. malayi* and *Loa loa* and probably those of *W. bancrofti*. However, this action is slower than the effect on microfilariae. The drug is effective in ascariasis but needs prolonged administration in this condition.

Absorption, fate and excretion: Diethylcarbamazine is rapidly absorbed from the gastrointestinal tract. Peak plasma levels are achieved within 3 hours. The drug is uniformly distributed in the body with the exception of fat. Most of the drug is metabolised in the body and the products eliminated in urine.

Adverse reactions: The side-effects include anorexia, nausea, vomiting, headache and drowsiness. These are rarely troublesome. Allergic reactions, due to release of foreign proteins in the tissues by the death of larvae or adult worms, include fever, tachycardia, lymphadenopathy, muscular pains and skin rashes. The allergic reactions may involve the eye. It is recommended, therefore, to start the therapy with a small dose and then increase it gradually. Severe ocular reactions can be controlled by instillation of 5 per cent hydrocortisone drops. Administration of dexamethasone 1 mg. with cyproheptadine 8 mg. given orally 12 hours before starting diethylcarbamazine has been demonstrated to diminish the incidence and severity of these allergic reactions without interfering with the therapeutic activity of diethylcarbamazine. Very high doses may cause muscle tremors and convulsions.

Preparations and dosage: Diethylcarbamazine citrate I.P. is a white, crystalline, hygroscopic powder with an acid and a bitter taste, extremely soluble in water. Diethylcarbamazine tablet, usually contains 50 mg. of diethylcarbamazine citrate. The syrup contains 10 mg./ml.

Therapeutic uses:

(1) *Filariasis*: In *W. bancrofti* and *Loa loa* infections, the recommended dose is 6-12 mg. per kg. body weight daily in single or divided doses for 3 weeks. For mass treatment in endemic areas, 6 mg. per kg. body weight given at weekly intervals to a total of 6 doses is effective.

(2) *Tropical eosinophilia*: The etiology of this condition is not known, but it is believed to be due to a parasite. The condition is characterised by fever, anorexia and attacks of dyspnoea resembling bron-

chial asthma, and is associated with leucocytosis and marked eosinophilia. Diethylcarbamazine in doses of 6-12 mg. per kg. body weight daily orally for 8 to 16 days is highly effective and is the drug of choice. Pentavalent organic arsenicals like carbarsone are also useful.

(3) In *onchocerciasis* and in *B. malayi* infections, treatment should be started with a dose of 0.5 mg. per kg. given once on the first day and twice on the second day. The dose is then increased to 2 mg. per kg. thrice daily. Treatment should be continued for a minimum period of 3 weeks.

In larva migrans (creeping eruption), a dose of 2 mg. per kg. is given daily for 10 to 21 days. Some physicians, however, prefer thiabendazole in this condition.

DRUG THERAPY OF GUINEA WORM

Dracunculus medinensis infestation is transmitted by drinking of water containing infected cyclops (water flea). The adult female usually remains in subcutaneous tissue and may come out through a small ulcer, usually on the foot. There is no specific drug remedy for guinea worm at present, and many indigenous preparations are claimed to be useful in helping easy expulsion of the worm by gradual pulling. Niridazole is effective in dracontiasis; the dose recommended is 25 mg./kg./day, in divided doses, for 10 days. Metronidazole has also been claimed to be equally effective in this condition. A single injection of Mel W (5 mg./kg. upto a total of 200 mg.) or thiabendazole, 100 mg. per kg. body weight, for one day by mouth are also claimed to be highly effective.

The most important treatment of dracontiasis, as in any other worm infestation, is mainly preventive. This is very simple as the intermediate host, cyclops, can easily be filtered out from the drinking water by using a piece of cloth.

55 Chemotherapy of Malignancy

In spite of voluminous work during the past decade, chemotherapy of malignant diseases remains still unfruitful as compared to the success achieved in chemotherapy of microbial infections. The problem of chemotherapy of malignancy, in some respect, differs basically from that of chemotherapy of infections. Thus;

(a) in infections, the invading microbe is biologically 'foreign' to the host and its metabolic reactions are so different from those of the host tissue cells that a chemotherapeutic agent can attack it selectively, without affecting the host tissue cells. No such clear cut differences in metabolic reactions have been demonstrated between malignant and normal cells; drugs probably destroy the cancerous tissue because it is a growing tissue and the fact that it is also malignant may not be relevant. Thus, the anticancer drugs lack the specificity of antimicrobial drugs and have a lower margin of safety.

(b) In infections, the body helps the antimicrobial drug with its own defence system in the form of antibodies, phagocytosis etc. Although antibodies have been demonstrated against certain cancer cells, such host defence is usually lacking or ineffective. It is necessary, therefore, to use the anticancer drugs in such doses as to destroy all the malignant cells. This is impracticable at present because of non-specificity and high tissue toxicity of these compounds. Hence, even after satisfactory initial treatment, the possibility of recurrence always remains.

(c) Neoplastic cells can develop resistance to drugs.

Perhaps, the ideal way to treat the malignant disease is to correct or modify those factors which initiate and maintain the metabolic change which converts a normal cell into a malignant one. Unfortunately, no definite data are available which differentiate a normal cell from a malignant one. Hence, all the anticancer compounds presently available are mainly palliative in action (except in a few cases) and wherever possible, surgery is usually to be preferred, with or without chemotherapy.

Laboratory evaluation of antimalignancy drugs: Drugs with potential anticancer properties are tested usually in mice or rats with induced tumours and virus-induced leukemias. Commonly, tumours are transplanted into these animals; occasionally, animals with spontaneous or chemically induced tumours are used. Various laboratories have now preserved a variety of tumours like mammary carcinoma, melanoma and lymphosarcoma for many generations, which can be transplanted into animals. Drugs can be assayed quantitatively for their capacity to inhibit the growth of such transplanted tumour. Although these tests show whether a drug can inhibit the growth of cancer cells or not, they do not give any indication regarding their mode or specificity of action. Often, drugs which are effective against one or more transplanted tumours are ineffective or very toxic in human malignant diseases.

The drugs commonly employed in the treatment of malignant diseases can be classified according to their mode of action as follows:

I. **Alkylating agents:**

(a) Nitrogen mustards e.g. Mechlorethamine, Cyclophosphamide, Melphalan, Uracil mustard and Chlorambucil.

(b) Ethylenimines e.g. Triethylenemelamine (TEM), Triethylene thiophosphoramide (Thio-TEPA).

(c) Alkyl Sulfonates e.g. Busulfan.

II. **Antimetabolites:**

(a) Folic acid antagonists e.g. Methotrexate (amethopterin).

(b) Purine antagonists e.g. 6-mercaptopurine, Azathioprine.

(c) Pyrimidine antagonists e.g. Fluorouracil, Fluorodeoxyuridine, Cytosine arabinoside.

III. **Radioactive isotopes** e.g. Radioiodine, Radiogold, Radiophosphorus.

IV. **Antibiotics** e.g. Actinomycin-D, Mitomycin-C, Rubidomycin, Adriamycin, Bleomycin, and Mithramycin.

V. **Miscellaneous agents:**

(a) Vinca alkaloids—Vinblastine, Vincristine.

(b) Others: Procarbazine, o, p DDD, 1-Asparaginase, Streptozotocin.

VI. **Hormones:** Androgens, estrogens, progestins and corticosteroids.

ALKYLATING AGENTS

The compound sulfur mustard was first used by the Germans in 1917 in chemical warfare against the British. It caused severe vesication of the skin and the mucous membranes, gastrointestinal ulcerations and depression of the bone marrow. The pharmacological properties of nitrogen mustards and their possible therapeutic application were made known only after the termination of World War II (1946).

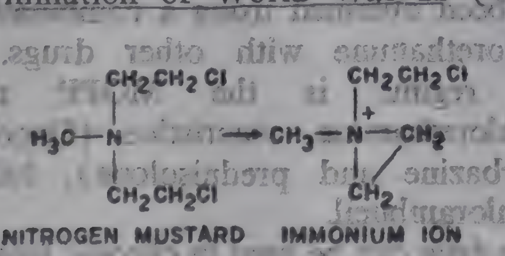


Fig. 55.1: Mechanism of action of nitrogen mustard

Mechanism of action: Nitrogen mustards are called alkylating agents because these compounds can transfer an alkyl radical to a suitable receptor site. Alkylating agents, in neutral or alkaline solutions, form highly reactive quaternary ammonium derivatives, ethylenimmonium cations (Fig. 55.1). These cations react with (alkylate) groupings like amino, sulfhydryl, hydroxy or phosphate in the physiologically important molecules in the cells and render them unavailable for the normal metabolic reactions. All the therapeutically used alkylating agents have more than one active alkylating group per molecule; depending upon this number, the compounds are termed as di- or polyfunctional.

The compound mechlorethamine, when dissolved in water, undergoes this intramolecular transformation immediately. Hence, it is supplied in dry powder form and a solution is prepared just prior to its intravenous use.

The ethylenimine derivatives like TEM act similarly as nitrogen mustards. The alkyl sulfonate compounds like busulfan, however, react with sulfhydryl group resulting in removal of the sulfur from the latter (sulfur stripping).

Alkylating agents, being nucleophilic react with the nucleic acid bases and inhibit DNA synthesis. They also bring about a cross-linkage of DNA strands in resting as well as in dividing cells and thus interfere with cell replication.

Pharmacological actions: The common pharmacological actions of various alkylating agents are discussed below. Important individual differences are mentioned under each drug.

(a) **Cytotoxic action:** In general, these drugs damage the nuclei of growing and multiplying cells. The hemopoietic system is highly susceptible to this action. Thus, they cause leucopenia, anemia, thrombocytopenia and in toxic doses, aplasia of the bone marrow. Although the net result is similar, the mode of action of individual drugs may differ in some detail. Thus, chlorambucil is more effective against the cells of lymphoid series while busulfan has predominant action against myeloid tissue.

These drugs also affect epithelial tissues such as those of cornea and the intestinal mucosa. They cause mitotic arrest, pyknosis, nuclear fragmentation and desquamation, leading to the formation of ulcers. Hair follicles are also damaged causing alopecia. These drugs may impair spermatogenesis in males and may cause amenorrhoea in females by damaging the germinal epithelium of the gonads.

(b) **Immunosuppressant action:** Alkylating agents suppress antibody production and the immune response.

(c) **Miscellaneous actions:** In very high doses, not employed therapeutically, nitrogen mustards can cause stimulation of the CNS, vomiting and death. In therapeutic doses, all the alkylating agents produce nausea and vomiting.

The actions produced by nitrogen mustards resemble to some extent the biological effects produced by ionizing radiation. Thus, both ionizing radiation and nitrogen mustards:

(i) cause intestinal and hematological changes,
(ii) suppress antibody formation,
(iii) inhibit cell division and growth,
(iv) cause foetal abnormalities,
(v) induce genetic mutations,
(vi) are effective against similar types of neoplasms, and
(vii) show a dose response relationship, larger doses being more effective than smaller doses.

Hence, nitrogen mustards are also called as *Radiomimetic drugs*. All alkylating agents, however, are not radiomimetic to the same extent e.g. a drug like busulfan is radiomimetic only to a limited extent.

MECHLORETHAMINE (Mustine): This is supplied as hydrochloride, 10 mg. of which are triturated with 90 mg. of anhydrous sodium chloride to increase the bulk. Locally, it is a vesicant, the most susceptible tissues being those of the skin, the eyes and the respiratory tract.

The drug can get absorbed by oral route but causes severe irritation and hence, is always given intravenously. When dissolved in water, the drug undergoes very rapid chemical transformation within a few minutes and hence, must be given immediately. It is largely metabolised in the body and very little, less than 0.01 per cent, is excreted in the urine.

The drug is dissolved in 10 ml. of distilled water just prior to injection. Since it is a powerful local irritant, it is injected into the tubing of a rapidly running intravenous infusion. This reduces the irritation of the intima of the vein. Extravasation of the drug in the tissues causes severe irritation, necrosis and sloughing.

The usual total dose is 0.4 mg./kg. of body weight given either singly or in 2 to 4 divided portions. It should not be repeated unless the bone marrow function has recovered; this usually takes at least 4 to 6 weeks.

Adverse reactions: Locally, it can cause thrombophlebitis. Commonly, it produces anorexia, severe nausea and vomiting. Hence, it is usually administered at bed time and prophylactically an antiemetic like chlorpromazine may be used. Delayed toxicity involves anemia, severe bone marrow depression, aplasia and death. It can cause menstrual irregularities in females. The drug should be avoided during pregnancy for fear of causing foetal abnormalities.

Therapeutic uses: Mechlorethamine is most useful in Hodgkin's disease and to a smaller extent in other lymphomas.

In Hodgkin's disease, prolonged remissions have been obtained using a combination of mechlorethamine with other drugs. One such regime is the MOPP regime (mechlorethamine, vincristine (Oncovine), procarbazine and prednisolone), followed by chlorambucil.

The drug can be used in chronic leukemia, bronchogenic, ovarian and other carcinomas, seminomas, mycosis fungoides and multiple myelomatosis; but other agents are generally preferred in these conditions.

CYCLOPHOSPHAMIDE (Endoxan): The pharmacological actions of this compound are mostly similar to those of mechlorethamine hydrochloride. Before acting, it is converted in the blood or the liver to its active form.

As compared to nitrogen mustard it is not a local irritant or a vesicant. Further, it can be given orally as well as parenterally and is less likely to cause thrombocytopenia. However, it has a greater tendency to cause alopecia.

Cyclophosphamide is well absorbed from the gastrointestinal tract. The exact metabolism in the body is not known. About 14 per cent of the drug appears in the urine in unchanged after intravenous injection.

Toxicity of cyclophosphamide is similar to that of mechlorethamine. Sometimes, it causes chemical cystitis and hepatic damage.

Preparations and dosage: Cyclophosphamide is supplied as 50 mg. tablets or vials containing 100-200 mg. of powder for injection. Solution for injection is prepared by adding 5 ml. of sterile water to 100 mg. of the drug. Unlike mechlorethamine, the solution remains stable for 3 hours. The drug can be given intravenously, intrapleurally, intraperitoneally, intra-arterially and directly into the tumour. The usual daily dose is 2-3 mg per kg. orally or intravenously for 6-8 days, followed by the daily oral maintenance dose of 100 mg. for 30-40 days. It can be repeated after 6-8 weeks. Some authorities have used large single doses in certain resistant cases of lymphomas. Prolonged therapy with cyclophosphamide must be guided by regular leucocytic counts.

Therapeutic uses: These are similar to those of mechlorethamine. As it is excreted partly unchanged in urine, it can cause hemorrhagic cystitis. This can be prevented by advising the patient to take plenty of fluids. It is, however, preferred to mechlorethamine because it is non-irritant and effective orally. Further, when cyclophosphamide is used as a part of a multiple-drug regime, long term remissions have been obtained in children with acute leukemia.

Its use as an immunosuppressing agent is discussed in Chapter 70.

MELPHALAN (Alkeran, 1-Sarcolysin): This is a phenylalanine nitrogen mustard and has properties similar to the other alkylating agents. It is effective orally. It is less irritant locally and alopecia is rare following its use. Usually, it causes nausea. Other systemic toxic effects are similar to those of mechlorethamine.

Melphalan is administered orally in 2 mg. tablets; the total dose recommended is 4-6 mg. daily for about 2-3 weeks followed by a rest period of at least four weeks. The drug is claimed to be more useful in multiple myeloma and breast cancer.

URACIL MUSTARD: This compound has similar properties as mechlorethamine. It can, however, be given orally and is less irritant. The dose recommended is 1-2 mg. daily for three weeks followed by a rest period of 1-2 weeks.

CHLORAMBUCIL (Leukeran): This compound, chemically related to mechlorethamine, has similar pharmacological and toxicological properties, including the action on the central nervous system.

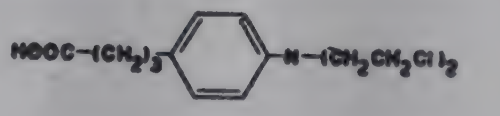


Fig. 55.2: Chlorambucil

Chlorambucil, however, is the shortest acting nitrogen mustard. It is effective orally predominantly against malignant cells of lymphoid series. It is not a local irritant and is less likely to cause alopecia even after prolonged use. Its myelosuppressive effect is also less.

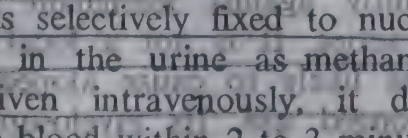
Chlorambucil is supplied as 2 mg. tablets. It is given orally, usually in dose of 0.1-0.2 mg. per kg. of body weight daily for 3 to 6 weeks.

Therapeutic uses: The drug can be used for similar purposes as cyclophosphamide but is the drug of choice in the treatment of chronic lymphocytic leukemia.

TRIETHYLENEMELAMINE (TEM): This orally effective agent has actions similar to those of nitrogen mustards but it causes less nausea and vomting. The drug, however, gets firmly bound to food and is irregularly absorbed. It is now used in the treatment of retinoblastoma.

THIO-TEPA: This compound has similar actions as mechlorethamine but is not a local irritant. It is not well absorbed orally. It is the agent of choice for direct infiltration into tumours and for intracavitary injection.

BUSULFAN (Myleran): This drug differs from nitrogen mustards both in its chemical structure (Fig. 55.3) and in its mechanism of action. Therapeutically it is more effective against cells of the myeloid series. In low doses, the drug causes a selective depression of granulocyte and platelet production; it does not have a significant action on the intestinal epithelium or the lymphoid tissue. In combination with chlorambucil, it can produce actions similar to radiation.



$$H_3C-\overset{\overset{O}{\|}}{\underset{\underset{O}{\|}}{S}}-O-(CH_2)_4-O-\overset{\overset{O}{\|}}{\underset{\underset{O}{\|}}{S}}-CH_3$$

Fig. 55.3: Busulfan

Absorption, fate and excretion: Busulfan is given orally. It is well absorbed. The drug gets selectively fixed to nuclei. It is excreted in the urine as methanesulfonic acid. Given intravenously, it disappears from the blood within 2 to 3 minutes.

Adverse reactions: These are similar to those of other alkylating agents. It causes much less nausea. Because of its selective action, the incidence of thrombocytopenia is higher. Prolonged administration of busulfan may cause amenorrhoea and diffuse skin pigmentation. Rarely, it can cause wasting and pigmentation resembling Addison's disease, anhidrosis and pulmonary fibrosis.

Therapeutic uses: It is the drug of choice in the treatment of chronic myeloid leukaemia. It is administered orally in 2 mg. tablets. The treatment is initiated with 4-12 mg. daily and then, depending upon the leucocytic count, the dose is tapered to a daily maintenance dose of 1-3 mg.

ANTIMETABOLITES

Chemical substances which take part in cellular metabolic reactions are called as metabolites. An antimetabolite is a chemical agent which, by virtue of its close structural similarity to the metabolite, blocks its actions. It can achieve this either by preventing the combination of the metabolite with its specific enzyme or by itself combining with the specific enzyme and thus getting transformed into a compound which is either metabolically inactive or harmful to the cell. The latter process is sometimes called as *lethal synthesis*.

Clinically useful growth inhibiting antimetabolites are structural analogues of (i) substances essential for the synthesis of the nucleic acid bases e.g. folic acid antagonist or (ii) substances which get incorporated into the nucleic acid chains and act as pseudometabolites e.g. 6 mercaptopurine.

METHOTREXATE (Amethopterin): This is a 4-amino substituted folic acid analogue which acts as a folic acid antagonist.

Mechanism of action: Folic acid is essential for the production of the coenzyme, tetrahydro-folic acid (THF). The conversion of folate to THF is carried out by an enzyme, folate reductase. Methotrexate competes with folic acid for this enzyme and succeeds in binding the folate reductase irreversibly, thus restricting the production of THF. Since the antimetabolite itself cannot function as THF, lack of the coenzyme THF leads to inhibition of DNA synthesis and consequently of cell replication; such cells eventually die. Methotrexate is, therefore, more toxic to tissues with a higher proportion of rapidly dividing cells, such as the bone marrow.

Pharmacological actions: Methotrexate has a predominant action on the bone marrow. It inhibits the erythropoiesis, myelopoiesis and finally may cause aplasia of the bone marrow. This causes marked peripheral granulocytopenia, reticulocytopenia and moderate lymphopenia. The drug also causes ulceration of the intestinal mucosa leading to severe hemorrhagic, desquamating enteritis. It can cross the placental barrier and may interfere with embryogenesis leading to foetal abnormalities and death. Certain immune reactions are also inhibited.

Absorption, fate and excretion: Methotrexate is well absorbed from the intestines. The drug, after entering the cell, does not leave it until the cell dies. It thus causes a prolonged inhibitory effect. About 50-90 per cent of the dose is rapidly excreted in the urine, in free form. Renal functional impairment is a contraindication to its use.

The metabolism of methotrexate differs in some respects from that of folate. Thus, it disappears from the blood rapidly and remains in the tissue longer than folate. Its concentration in the CSF, however, is poor.

Adverse reactions: These are due to deficiency of THF and include megaloblastic anemia, thrombocytopenia, leucopenia, aplasia, intestinal ulceration and diarrhoea; alopecia, dermatitis, ulcerative stomatitis and liver damage. These cannot be reversed by giving folic acid as its conversion to THF is blocked. Hence, ideally THF should be administered to antagonise the toxicity of methotrexate. This substance, however, is too unstable for therapeutic use and hence, a related compound folinic acid (N^5-formyl THF, citrovorum factor) is used. Folinic acid does not displace the already fixed methotrexate but supplies a form of THF which is utilizable by the cells. Folinic acid is usually given intramuscularly in the dose of 3 to 6 mg. daily, in the form of its calcium salt.

Preparations and dosage: Methotrexate is supplied as 2.5 mg. tablets and as powder for injection. Daily recommended dose for children is 2.5 to 5.0 mg. and for adults 2.5 to 10 mg. In case of choriocarcinoma, larger doses of 10-30 mg daily for five days are usually given. Methotrexate can be given intrathecally, to treat meningeal infiltration in acute leukemia, in a single dose of 0.1-0.5 mg. per kg. body weight.

Therapeutic uses: It is used in acute lymphatic leukemia in children. It is extremely useful in choriocarcinoma, where it has almost produced 'cure' in certain cases. It has some place in the treatment of soft tissue sarcoma, breast cancer, in acute myeloid leukemia and a skin condition called psoriasis.

6-MERCAPTOPURINE (Puri-Nethol): This analogue of purine probably acts by interfering with the synthesis and interconversion of purines. 6-Mercaptopurine is converted in the cells to ribonucleotide of 6-mercaptopurine, which then suppresses the *de novo* biosynthesis of purines and hence of DNA. The drug is mainly toxic to the bone marrow and intestinal epithelium. Its pharmacological actions are similar to those of methotrexate.

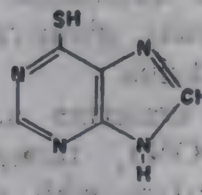


Fig. 55.4: 6-Mercaptopurine

Absorption, fate and excretion: The drug is well absorbed after oral administration. It is metabolised rapidly by the xanthine oxidases, which also synthesize uric acid. Use of a xanthine oxidase inhibitor like allopurinol decreases the inactivation of 6-mercaptopurine. Mercaptopurine and its metabolites are rapidly excreted by the kidneys. Penetration by this compound into the CSF is poor.

Adverse reactions: These are similar to those of methotrexate and are mainly related to bone marrow and gastrointestinal tract. Sometimes, it causes hepatic necrosis. It may also cause hyperuricemia with hyperuricosuria due to massive destruction of the cells of lymphoid tissues. Hence, urine should be maintained alkaline and its volume adequate.

Therapeutic uses: Mercaptopurine is useful in the treatment of acute leukemia, particularly in children. It is supplied as 50 mg. tablets. The usual daily oral dose is 2.5 mg. per kg. given as a single dose. It is regulated by noting the hematological and clinical improvement. Mercaptopurine is also effective in chorio-carcinoma and chronic myelogenous leukemia. The drug acts more slowly than methotrexate. Repeated use may lead to the development of resistance. However, cross resistance between 6-mercaptopurine and other antileukemic drugs like methotrexate does not occur; this is a great clinical advantage.

Other purine analogues like 6-thioguanine and azathioprine also possess cytotoxic actions. However, they do not seem to have any distinct advantages over mercaptopurine as antileukemic agents. Azathioprine (Imuran) is usually favoured as an immunosuppressive agent in organ transplantation and in certain autoimmune diseases like hemolytic anemias, glomerulonephritis and rheumatoid arthritis.

Drugs like azaserine and duazomycin (N—acetyl DON), though not purine analogues, interfere with purine synthesis by acting as glutamine antagonists. However, clinically they are not so useful.

FLUOROURACIL: This is a fluorinated analogue of pyrimidine. The drug probably acts by binding the enzyme thymidilate synthetase, thus preventing the production of thymin, the basic component of DNA. It also gets incorporated into RNA in place of uracil. Like other antimetabolites, it is toxic to the bone marrow and the alimentary epithelium. It is usually administered intravenously to prevent its degradation in the liver. Fluoro-uracil and its derivative, fluoro-deoxyuridine have been used by slow intravenous infusion in the treatment of carcinoma of stomach, colon, rectum, breast and ovaries. The dose recommended is 15 mg./kg. body weight daily for 3-5 days, followed by 7.5 mg./kg every second or third day till toxicity is seen. It is available as solution 50 mg./ml in 10 ml. containers.

CYTOSINE ARABINOSIDE: This pyrimidine analogue is considered to be the drug of choice in inducing remission in acute myeloid leukemia, especially in adults. The toxic effects include nausea, vomiting and depression of the bone marrow.

Radioactive Isotopes

These are the isotopes of various elements which act because of their physical property of giving radiation. The radiations given out produce ionization in the cells, thereby disrupting the cellular metabolism, ultimately leading to cell destruction. Radio-isotopes are discussed in detail elsewhere. The therapeutically useful radioisotopes are radioiodine—^{131}I, radiogold ^{198}Au, and radio-phosphorus ^{32}P.

RADIOIODINE (Na ^{131}I): This is useful in certain cases of thyroid carcinoma. The drug is given as Na ^{131}I orally in doses of 100-200 milicuries. Usually, in thyroid carcinoma, surgery is to be preferred with or without radiation. Only those malignant tumours which can concentrate enough iodine e.g. follicular carcinoma, can be destroyed by this therapy. Radioiodine acts by giving beta radiation. It has a half life of 8.04 days.

Combined therapy with surgery followed by radioiodine can achieve excellent results in selected cases. Usually, the patient is allowed to develop myxedema before the administration of radioiodine. This ensures the maximum uptake by the left-over "thyroid tissues". Generally, 2-3 doses of 150 mc. each at the interval of 2-3 months are considered adequate and the total dose should not exceed 500 mc. except on rare occasion, for the fear of development of leukaemia. During radioiodine therapy, the patient must be isolated and special arrangements made for the disposal of urine in order to reduce the possible radiation hazards to other people. Radioiodine is discussed in Chapter 58.

RADIOACTIVE PHOSPHORUS (Sodium phosphate ^{32}P): Radioactive phosphorus is a beta emitting isotope with a half life of 14.3 days.

It is metabolized by the body like stable phosphorus and is distributed in different tissues in proportion to their total phosphorus content. It is taken up rapidly by those cells where the metabolic turnover of phosphorus is high e.g. multiplying cells, bone marrow, spleen and lymph nodes. It is deposited in bones and is incorporated in nucleo-proteins of growing cells. Because of its wide distribution, it causes generalised body irradiation including that of lungs, gastrointestinal tract and gonads. Excessive irradiation of bone marrow may cause leucopenia, thrombocytopenia and anemia.

It is administered in the form of sodium phosphate-^{32}P, either orally or intravenously.

Therapeutic uses: The most important use of radiophosphorus is in the treatment of polycythemia vera, where it is used alone or with phlebotomy. The drug is given orally in doses of 5-6 mc. About 25 per cent of the dose is not absorbed and appears in feces. It suppresses the production of RBCs, platelets and leucocytes; it does not destroy the already formed mature red blood cells. Hence, therapeutic effect is seen after an interval of 6-8 weeks. It can be given intravenously in dose of 2.5 mc. The drug may be repeated, if necessary, after 3-4 months.

Repeated doses of ^{32}P in a case of polycythemia vera may sometimes cause acute leukemia in these patients and hence, some authorities prefer to avoid this therapy. However, it appears on the present evidence that in polycythemia vera, its advantages outweigh its risks and that it is the drug of choice in most cases.

The other agents which are used in this condition are busulphan and chlorambucil.

RADIOACTIVE GOLD (^{198}Au): This radioisotope, with half life of 2.69 days, gives out low energy beta and gamma radiations. Because of its beta radiations, it is used to produce localized tissue destruction.

Radiogold is used as sterile colloidal gold solution prepared in excess gelatin, with vitamin C as a reducing agent and pH adjusted to 5.5-6.5. In this form, the gold does not ionize and remains biologically relatively inert. The solution is deep cherry red in colour.

When injected into a body cavity, because of its colloidal nature, very little gold enters the blood and hence, it produces local irradiation. Large portion becomes fixed on the superficial serous surface. Phagocytes carrying gold particles are carried to the lymph nodes, where it helps to irradiate regional lymph nodes.

Therapeutic uses: Radiogold is used as a palliative measure in the treatment of malignant pleural and peritoneal effusions. These conditions are usually inoperable and radiogold helps in reducing the accumulation of fluid. It is administered in the dose of 100-150 mc. depending upon the extent of the lesion.

Radiogold can also be used directly into the tumours which are inoperable e.g. in prostatic and pelvic cancers.

In all these cases, radiogold, rarely prolongs the life though it gives symptomatic relief.

Dangers of radiation therapy are discused elsewhere.

ANTIMALIGNANCY ANTIBIOTICS

ACTINOMYCIN D: This is an antibiotic obtained from the species streptomyces. It acts by blocking DNA-dependent RNA synthesis. Its value in therapeutics, however, is limited as it is relatively toxic. It is mostly used as an experimental tool to block the production of ribosomal ribonucleic acid in cell metabolism studies.

Actinomycin D has toxicity similar to that of mechlorethamine. It can damage the skin, particularly that exposed previously to x-ray irradiation.

The drug is given intravenously, by injecting it into the tubing of a freely running infusion, in the dose of 15 microgrammes per kg. daily for five days. It is mainly excreted in the bile and little appears in the urine.

Actinomycin in combination with irradiation, has been found to be useful in cases of Wilm's tumour, choriocarcinomas and Hodgkin's disease resistant to other drugs.

MITOMYCIN C: This antibiotic, obtained from *Streptomyces Caespitosus* has cytotoxic properties similar to those of the polyfunctional alkylating agents. It has been employed by intravenous or intra-arterial injection, in the treatment of chronic myeloid leukemia and Hodgkin's disease. Like alkylating agents the drug may cause local tissue necrosis on extravasation, severe bone marrow depression, bleeding and toxic hepatitis. The usual total dose in man is about 1 mg./kg. of body weight given I.V. in 4-10 daily injections.

RUBIDOMYCIN (Daunomycin, Daunorubicin): This antibiotic, obtained from a strain of *Streptomyces Coeruleorubidus*, is also cytotoxic and when used along with vincristine and prednisolone has been reported to produce remissions in majority of the cases of acute leukemia in children. It is also useful in acute myeloblastic leukemia in adults. It acts by inhibiting DNA dependent RNA synthesis. It causes profound bone marrow depression, may produce allergic reactions and is highly toxic to the myocardium. Because of this, it is not used for maintenance therapy.

DOXORUBICIN (Adriamycin): This is an antitumour antibiotic obtained from *Streptomyces pneuceticus* and resembles daunorubicin in its chemical structure. It has been claimed to produce a complete remission in acute lymphoblastic leukemia and lymphoblastic lymphosarcoma in patients who failed to respond to or had relapsed after stopping standard chemotherapy. It has also been used in other malignancies. It is used intravenously in the dose of 0.4 mg./kg. once daily for 2-3 days.

BLEOMYCIN: This drug, derived from *Streptomyces Verticillus*, is useful in epidermoid carcinomas of the skin, the upper respiratory passages, the oral cavity and the genito-urinary tract and in lymphomas resistant to other drugs. Radiation can be given after bleomycin but prior radiation impairs its effectiveness. Its main toxicity is pneumonitis occasionally progressing to pulmonary fibrosis and death, nausea, vomiting, dermographic and scleroderma like changes in the skin. It is used in the dose of 10 to 20 units per square meter body surface area intravenously, intramuscularly or subcutaneously twice a week. A maintenance dose is usually 5 units once weekly.

MITHRAMYCIN: This drug derived from *Streptomyces plicatus* is believed to act by interfering with RNA synthesis. It has high toxicity and causes myelosuppression, liver and kidney damage and bleeding due to suppression of clotting factors. It has been found to be useful in embryonal cell carcinoma of the testis (in the dose of 25 μg./kg./day intravenously for 10 days), in hypercalcemia due to malignant disease (25 μg./kg. intravenously once or twice) and in Paget's disease (25 ug/kg. intravenously once a week). The lower dose regimes are relatively safer than the one required for the first condition. The drug is highly toxic.

MISCELLANEOUS DRUGS

VINCA ALKALOIDS: From the various alkaloids isolated from periwinkle plant (*Vinca rosea; Catharanthus rosens*), two compounds, vinblastine sulfate and vincristine sulfate, have been shown to be useful in the chemotherapy of malignancy.

Mechanism of action: These drugs inhibit mitotic spindle formation. The exact mechanism of their action, however, is not clear; but it probably concerns an area of cellular metabolism different from that affected by irradiation or alkylating agents.

Pharmacological actions: Both these alkaloids inhibit the growth of various experimental tumours and have similar spectrum of activity. Interestingly, there is no cross resistance between these two agents, in spite of the close similarity in their chemical structure. Like other cytotoxic drugs, they also cause bone marrow depression, alopecia and toxic effects on oral and gastrointestinal mucosa.

In addition, vinca alkaloids produce certain neurological effects. They affect the neuromuscular transmission and cause peripheral neuropathy. They may also cause mental depression, ataxia and tremors. It should be noted that the molecules of these alkaloids contain indol and dihydroindole groups, similar to other psychotropic and neurotoxic drugs like reserpine and LSD.

Because of their large molecular size, vinca alkaloids are not well absorbed by oral route. These drugs, being highly corrosive, are administered through a freely running intravenous infusion. Vinca alkaloids are excreted primarily by the liver into the biliary tract.

Adverse reactions: Although these drugs are chemically closely related, their toxicity is relatively different. Thus, vinblastine is more toxic to the bone marrow while vincristine causes more neurotoxicity and alopecia. Common toxic effects include nausea, anorexia and vomiting, mental depression, constipation and alopecia. Neurotoxicity includes cranial nerve palsies, peripheral neuropathy, and psychosis and signs of intestinal obstruction due to severe constipation with paralytic ileus. They have been shown to be teratogenic in animals.

Therapeutic uses: The commonly employed drug is vinblastine sulfate (Velban) supplied as 10 mg. of the dry powder. The dose recommended is 0.1 mg. per kg. body weight once a week, raised by 0.05 mg. at weekly interval, if satisfactory response is not obtained after the previous injection. The drug should not be used unless the total WBC count is at least 4000 per cmm.

Vinblastine is mainly useful in Hodgkin's disease where it produces remission in 50-60 per cent of cases. It can also be used in methotrexate resistant choriocarcinoma and lymphosarcoma. Its therapeutic usefulness in other malignant conditions is very limited.

Vincristine (Oncovin) is useful in the treatment of acute lymphatic leukemia in children to initiate remission. In children, the weekly intravenous dose varies from 0.03 to 0.15 mg. per kg. For adults, a dose of 0.025 to 0.075 mg. per kg. a week is usually employed.

PROCARBAZINE HYDROCHLORIDE (Matulane, Natulan): This drug has been found to be effective orally in the treatment of Hodgkin's disease. The toxic effects reported are restlessness, drowsiness, disorientation, leucopenia, thrombocytopenia and anemia. The bone marrow toxicity usually develops in the 3rd week of therapy. The initial daily dose of the drug is 50 mg. increased gradually to 300 mg. per day, given in 2 or 3 divided portions. The patient may be maintained on 50 mg. daily after satisfactory remission.

o, p. DDD: This substance, structurally related to the insecticide DDT, gets selectively concentrated in the adrenal cortex and hence, has been used in the treatment of Cushing's syndrome due to malignant neoplasms of the adrenal cortex. The side effects encountered include anorexia, nausea, somnolence and lethargy. Most patients who receive the drug for more than a week require supportive therapy with a synthetic glucocorticoid to prevent the development of adrenal deficiency. The drug is administered orally in the daily dose of 8 to 10 g. for a period of 4 to 8 weeks, followed by 3 to 4 g. daily as the maintenance dose.

1-ASPARAGINASE: This enzyme, which deaminates asparagine to aspartic acid is prepared from *E. coli*. Asparagine is a non-essential amino acid normally synthesized by the mammalian tissue cells. Certain malignant tumours, however, are unable to synthesize asparagine and consequently, are dependent on supplies from the host. Asparaginase is believed to act by depleting asparagine from the host, thus denying the malignant cells, the essential metabolite. The noteworthy feature of its action is its non-toxicity to normal dividing cells in comparison to the neoplastic ones. When administered intravenously, the enzyme has produced relief in some cases of lymphoblastic leukemia and reticulum cell sarcoma. It may cause pyrogenic reactions and sensitization. Unfortunately, asparginase has failed to fulfil its early promise as a tumoricidal agent with minimum toxicity in human cancer.

HORMONES AND ANTI-HORMONAL DRUGS

Hormones act differently from the cytotoxic drugs and hence can be usefully combined with them in certain malignancies. They do not directly kill the susceptible malignant cells, do not cause hyperurecemia and are slower in their effect. They may act in one of the several ways: (1) Inhibition of cell growth and differentiation e.g. androgens in breast cancer and estrogens in prostatic cancer. (2) Stimulation of differentiation of cells which then regain their ability to respond to the body's controlling and inhibitory influences e.g. estrogens in breast cancer in post-menopausal woman. They are effective in suppressing these breast cancers which have an estrogen binding protein in them. (3) Extension of their physiological action e.g. glucocorticoids cause lysis of normal and leukemic lymphocytes and are effective in acute lymphatic leukemia. They stimulate the granuloblasts and are therefore ineffective in acute myeloid leukemia. (4) Inhibition of the circulating concentration of a substance which stimulates the malignant cells e.g. thyroxine is believed to suppress certain thyroid cancers by inhibiting TSH secretion.

Pharmacology of these hormones is discussed elsewhere. Their application in the treatment of certain malignancies is discussed below.

ESTROGENS: Carcinoma of the prostate is probably androgen dependent and bilateral orchidectomy, in patients with prostatic carcinoma with secondaries, can produce marked improvement. Similar beneficial effects are obtained by the administration of estrogens. The best results are obtained by combining estrogens with orchidectomy.

Synthetic estrogens which are as effective as the natural ones but much cheaper, are preferred. Diethylstilbestrol is given in the dose of 5 mg. thrice daily for several days and then reduced to 1 mg. thrice daily. Adverse effects due to estrogen therapy are discussed in Chapter 61. In males, these mainly include sexual impotence and gynecomastia; this however, rarely matters as prostatic carcinoma usually occurs in the elderly.

Estrogens are also useful in the treatment of carcinoma of the breast in males and in postmenopausal females, especially when the malignant tissue obtained at surgery can be shown to contain specific estrogen receptors. The effect of hormonal therapy is usually slow and the treatment should be continued at least for 8-10 weeks before it is declared unsuccessful.

Similar palliation in above mentioned malignancies can also be obtained by radiation hypophysectomy using radioactive Yttrium-90 implants into the pituitary fossa.

PROGESTINS: The endometrial carcinoma in humans is believed to be due to prolonged unopposed stimulation by estrogens. Hydroxyprogesterone caproate and megestrol acetate have been used with success in metastatic endometrial carcinoma. The former is usually given intramuscularly in the dose of 1-3 g at weekly intervals, and the latter orally in the dose of 40 mg four times a day. Medroxyprogesterone has also been used for this purpose. (See also Chapt. 61)

ANDROGENS: Androgens have been found useful in the treatment of mammary carcinoma in premenopausal women. They are always combined with oophorectomy. They are especially helpful in women with bone metastases because they promote recalcification. Because of its weaker virilizing effects, fluoxymesterone has now largely replaced methyltestosterone for this purpose. Alternatively, testosterone propionate is given intramuscularly in the dose of 50-100 mg twice weekly. The effect is seen after 6-8 weeks. Adverse effects of androgens are discussed in Chapter 63.

It must be pointed out that *rarely* estrogens and androgens can cause acceleration of the malignant process.

ADRENOCORTICOSTEROIDS: Hydrocortisone, a glucocorticoid, and related synthetic compounds like prednisolone have been shown to be useful in following conditions:

(1) In acute lymphatic leukemia in children and in malignant lymphoma. This is due to their direct lympholytic effect. They suppress mitoses in lymphocytes. Steroids are not useful in the myeloid and monocytic types of acute leukemias.

(2) These steroids are also useful to prevent the accelerated erythrocytic destruction and thus prevent anemia in disseminated cancer patients; further they effectively counter the hemolytic and hemorrhagic complications (due to thrombocytopenia) accompanying chronic lymphocytic and myeloid leukemia and malignant lymphomas.

(3) They are also useful to control the hypercalcemia caused by certain tumours or following drug therapy of malignancies and

(4) They can be used in critically ill patients along with cytotoxic drugs to produce symptomatic relief and a sense of well being.

Prednisolone is generally used in doses of 60-100 mg. daily initially and then, depending upon the response, reduced to a maintenance dose of 20-40 mg. daily. Dangers of prolonged corticosteroid therapy are discussed elsewhere.

1-THYROXINE: Certain types of thyroid carcinomas are probably dependent on thyroid stimulating hormone (TSH). These have been shown to undergo regression following large doses of thyroxine which probably act by suppressing TSH secretion. 1-Thyroxine is given orally in the maximum tolerated dose, once daily, for life time.

NAFOXIDINE: This is a nonsteroidal estrogen antagonist, structurally related to clomiphene. Chemically, it is a diphenyldihydronaphthalene derivative and is devoid of androgenic, progestational and gonadotrophin-inhibiting properties. Experimentally, it has a marked *in vivo* inhibitory effect on transplanted estrogen dependent tumour in hamster. The drug inhibits the binding of labelled estradiol to normal estrogen dependent target organs. Recently, it has been used orally in the doses of 60-90 mg. three times a day, in patients with advanced breast cancer with beneficial results. Adverse reactions reported so far are mild and include dryness of skin, photosensitivity and loss of scalp hair. The drug is under evaluation.

Use of immunostimulants in cancer therapy is described in Chapter 70.

Drug Therapy of Malignant Diseases

Although chemotherapy has definitely

improved the outlook in this otherwise hopeless malady, treatment is still palliative in nature. It must be pointed out that in a few conditions, long term remissions can be obtained by appropriate chemotherapy. These are acute leukemia in children, Hodgkin's disease, choriocarcinoma in females, Wilm's tumour in children, neuroblastoma and rhabdomyosarcoma.

In majority of the conditions, however, chemotherapy, being purely suppressive, is recommended to help the patient to return to his near-normal mode of life. It is not usually recommended simply for prolonging the act of dying, in an otherwise very ill patient.

Since all the cytotoxic agents are potentially very toxic to normal tissues, the diagnosis must be firmly established before using these drugs.

The management of malignancies with various drugs needs experience and no practitioner can be expected to have had such an experience. The detailed discussion of management of individual disease is beyond the scope of this book. Certain principles, however, are outlined below:

(1) The choice of a drug in a given condition is listed in table 55.1. In most instances, the choice is empirical and is dictated by experience rather than by any rational considerations. Hence, it is liable to undergo a continual change. In general, irradiation is recommended in a localised malignant growth, along with palliative surgery, wherever possible. This, if carried out early, will probably prevent the spread and also will cause less damage to healthy tissues elsewhere. Irradiation is contraindicated in acute lymphatic leukemia, as the lymph nodes may undergo inflammatory enlargement resulting in pressure symptoms. Prophylactic use of cytotoxic agents is not to be recommended unless there is evidence of widespread involvement of various tissues.

(2) Nearly all cytotoxic drugs act by interfering with cell replication. It is possible to devise a combination of drugs acting by different mechanisms and providing greater benefit than single agents do individually. Thus, in certatin conditions such as acute leukemia and Hodgkin's disease, combinations of drugs have been found to be more effective in inducing and maintaining a remission than single drugs. Five year remissions have now been obtained in 50% of patients with acute lymphatic leukemia and ten year remissions

Table 55.1: **Drug Therapy of Malignancy**

Disease	Drug(s) of choice	Other drugs
Acute lymphatic leukemia	Vincristine with Prednisolone	Methotrexate, Mercaptopurine, Cyclophosphamide
Chronic lymphatic leukemia	Chlorambucil	Mechlorethamine, Uracil-mustard, Cyclophosphamide
Chronic myeloid leukemia	Busulphan	—Do— Radiotherapy
Hodgkin's disease and lymphosarcoma	Methotrexate, Vincristine, Procarbazine and Prednisolone	Cyclophosphamide Chlorambucil
Multiple myeloma	Melphalan	Cyclophosphamide, Prednisolone
Choriocarcinoma	Methotrexate	Mercaptopurine, Actinomycin D
Carcinoma of bronchus, ovary, breast	Cyclophosphamide	Fluorouracil, Methotrexate

in 25%. Perhaps, the latter may justifiably be called 'cure'.

(3) In experimental animals, the following have been found to affect the response to cytotoxic drugs: the route of administration of a drug, the intervals between successive doses and the sequence in which two or more drugs are given. The exact role of these factors in chemotherapy of human cancer is being worked out.

(4) A single dose of a cytotoxic drug kills *not a fixed number* of cancer cells *but a constant proportion* of those present. Hence, chemotherapy has the maximum chances of being curative when few tumour cells are present. It is now appreciated that once a clinical remission is obtained, continuation of chemotherapy (perhaps with a different drug than the one used for inducing the remission) in the presence of inapparent, residual disease is highly effective and, therefore, very important in practice.

(5) Generally, cytotoxic drugs are to be administered intermittently to allow the normal body tissues (especially the bone marrow) to recover from the adverse effects of the drug. High doses are preferred to low doses when intermittent therapy is used.

(6) Conditions like acute leukemia, certain sarcomas and Hodgkin's disease which show rapid progression need prompt attention, while a condition like chronic lymphatic leukemia, particularly in old people, may progress so slowly that patients may enjoy good health and can survive almost a normal span of life without any chemotherapy.

(7) In most cases, drugs have to be given in such doses that toxic effects are inevitable and these should be watched for. Patients should have regular hematological supervision and with drugs like methotrexate, evidence for damage to the alimentary epithelium should be looked for. As a rule, chemotherapy should not be given simultaneously with local irradiation.

(8) All anticancer drugs used presently have adverse effects; there is no such thing as a nontoxic agent. The most frequent are infections and hemorrhage due to bone marrow depression. Hyperuricemia which may result from the breakdown of large numbers of tumour cells can be prevented by using allopurinol which interferes with uric acid synthesis. This drug can also be used for similar purpose along with 6-mercaptopurine, but as it interferes with the metabolism of 6-mercaptopurine, the dose of the latter should be reduced. Allopurinol is discussed in Chapter 65.

(9) Cytotoxic drugs are usually contraindicated during pregnancy as they may cause abortions or foetal abnormalities.

(10) In choosing a drug regime one must always keep in mind its "cost effectiveness" as chemotherapy in general is expensive at present.

Chemotherapy in maligant conditions is only a part of overall approach to the care of patient with cancer. This must be supported by other measures such as:

(a) Maintenance of nutrition,

(b) Treatment of anemia, if necessary by blood transfusion,

(c) Protection against infection as these drugs can suppress the antibody formation and immune response,

(d) Relieving pain and anxiety, if any, by appropriate therapy,

(e) Occupational therapy and

(f) Adequate emotional support to the patient and the family. This is very important particularly in a condition like incurable cancer where physician can hardly do anything specific but watch helplessly.

The best results are generally obtained in patients in good nutritional state and without severe metabolic disturbances, infection or other complications. Ideally, the patient should have adequate hepatic, renal and bone marrow function, uncompromised by tumour invasion, previous chemotherapy or irradiation (especially of the spine or pelvis).

56 Antiseptics, Disinfectants, Insecticides and Pharmacotherapy of Skin Diseases

Sterilization can be defined as freeing an article, a surface or a medium, by removing or killing all micro-organisms, both in vegetative and sporing states.

Disinfection is the term used for destruction of the pathogenic organisms that may cause infection. If spores are killed during the process, only then is it equivalent to sterilization. Sterilization and disinfection can be achieved by physical and chemical methods. A *disinfectant* or *germicide* is a chemical substance which causes disinfection. It may be bactericidal or bacteriostatic. According to their specific properties, disinfectants may be classified into *bactericides*, *sporicides*, *viricides* and *fungicides*. Drugs toxic to the external parasites are called *ectoparasiticides*. An *antiseptic* is a chemical disinfectant (usually bacteriostatic in the concentration in which it is used) that can be safely applied to the skin or mucous membranes. Antiseptics and disinfectants are probably the drugs most widely employed by the lay public. The agents are used not only in the original form but are often added to easily available every day necessities like soaps, toothpastes and after-shave lotions. Besides their use in local infections unpenetrable to systemic chemotherapy, the chemical disinfectants have many other uses such as disinfection of excreta, fumigation of rooms and bedding, and sterilization of instruments (endoscopes) and complicated apparatus (heart lung machines and respirators) that cannot be sterilized by heat.

Classification:

(A) **Physical agents** such as heat in various forms, filtration, non ionizing and ionizing radiation.

(B) **Chemical agents:** The number of chemical agents available for these purposes is enormous and constantly growing. The agents show a great diversity in their chemical structure; a tentative classification is given below:

I. **Acids:** (a) Inorganic acids: Boric acid, chromic acid. (b) Organic acids: Benzoic acid, salicylic acid, mandelic acid, nalidixic acid.

II. **Alkalies:** Sodium and potassium hydroxide.

III. **Alcohols:** Ethanol and isopropyl alcohol.

IV. **Aldehydes:** Formaldehyde, methenamine, gluteraldehyde.

V. **Surfactants:** (a) *Anionic*: Soaps, sodium lauryl sulfate, sodium cetostearyl sulfate. (b) *Ampholytic* surfactants. (c) *Cationic*: Benzalkonium, cetylpyridinium, benzethonium, triclobisonium, etc. (d) *Nonionic*: Polysorbates.

VI. **Phenols and related compounds**: Phenol, cresol, chlorocresol, picric acid, hexylresorcinol, bithionol, thymol, hexachlorophane.

VII. **Halogens and halogen containing compounds:** (a) Chlorine and Chloramines. (b) Iodine, iodoform and iodophors.

VIII. **Oxidizing agents:** Hydrogen peroxide and other peroxides, sodium perborate, potassium and zinc permanganates.

IX. **Dyes:** Crystal violet, brilliant green, methylene blue, acriflavine, proflavine.

X. **Heavy metals:** Silver nitrate, mercurial compounds, etc.

XI. **Gases:** Ethylene oxide.

Mechanism of action: The chemical antiseptics and disinfectants act on the micro-organisms by one or more of the following mechanisms:

(a) Coagulation of the bacterial proteins;

(b) An alteration in the properties of

the bacterial cell wall;

(c) Binding of free sulfhydryl (—SH) groups essential for enzyme action; and

(d) Competition with essential substrates for the important enzymes in the bacterial cell.

Factors which determine the therapeutic efficacy of these agents are:

(a) *Drug concentration and its therapeutic index.* In general, antiseptic effect increases with a rise in concentration. Alcohol, however, is an exception and shows maximum antiseptic activity in a 70 per cent concentration. The potency of a particular concentration is meaningful only in relation to the tissue toxicity (Therapeutic Index). Presence of necrotic tissue or crust reduces the penetration of these agents and thereby lowers their effective concentration. Similarly, tissue proteins reduce the concentration of halogen-containing and metallic antiseptics by adsorption while anionic surfactants like soaps reduce the effective concentration of cationic surfactants by chemical neutralization. A heavy inoculum of the infecting organism necessitates a larger quantity of the antiseptic agent.

(b) *Species susceptibility*: Some forms, particularly spores and some species of bacteria, are resistant to many antiseptics. Viruses are susceptible to alkalis but resistant to phenol.

(c) *Temperature and duration of contact*: A limited rise in environmental temperature and prolonged contact can enhance antiseptic activity. For example a rise of temperature by 10°C generally doubles the antibacterial activity of chemical agents whereas it increases that of moist heat a hundredfold.

Requirements of an ideal antiseptic and disinfectant: Ideally, such an agent should have a wide antimicrobial spectrum and should preferably be lethal to the bacteria, viruses, spores, protozoa and fungi. It should be active in the presence of body fluids and tissue degradation products, and in acidic as well as in alkaline media. The agent should have a quick action, high penetrating power and chemical stability, and should be compatible with other antiseptics and disinfectants. If used for disinfection of surgical instruments, it should not corrode the metal. The agent should not cause local irritation or sensitization and should not interfere with healing. If absorbed into systemic circulation, it should be devoid of serious toxic effects and it should be cheap. No such ideal agent, however, is available.

HEAT

Heat applied at the right temperature and for the correct period of time is the most important sterilizing agent available. It may be applied either in the form of moist heat or dry heat. Moist heat kills micro-organisms by coagulating the proteins. Dry heat kills them by oxidizing their cell constituents; this occurs at a much higher temperature than that at which coagulation of proteins occurs.

Moist heat can be applied in several ways:

(1) *Pasteurization*: which is commonly used to kill the pathogenic micro-organisms (but not spores nor all bacteria) in milk and certain vaccines.

(2) *Boiling in water*: Spores are often resistant to boiling at 100°C which can, therefore, be regarded at the best as a means of disinfection rather than of sterilization.

(3) *Steam*: Steam is a very efficient means of sterilization because of its high penetrating capacity and because it gives up a large amount of heat (latent heat) to the surface with which it comes into contact and on which it condenses as water. Steam may be used at atmospheric pressure (temperature 100°C) to sterilize culture media that decompose at higher temperatures. More commonly, steam is used at higher pressures which raise its temperature to between 108° and 147°C. By selecting the correct temperature and time cycle a wide variety of materials can be sterilized by this method: dressing

packs, surgical instruments, laboratory equipment, culture media and pharmaceutical products. Instruments which use steam under pressure for sterilization are called autoclaves. The main disadvantages of autoclaving are the blunting of sharp surgical instruments, condensation of steam on lenses in endoscopes and the damage heat causes to the cementing material in the latter and to certain rubber goods.

Dry heat can be used in several ways,

(a) *Flaming*: i.e. direct heating in a bunsen flame, is commonly used in a bacteriology laboratory to sterilize inoculating wires, points of forceps, etc.

(b) *Incineration*: i.e. burning to ashes, is suitable for soiled dressings, pathological material, animal carcasses and heavily soiled bedding. Certain types of plastics (polystyrenes) emit dense fumes during incineration and cannot be dealt with by this method.

(c) *Hot air* in an oven is commonly used to dry sterilize glass syringes and instruments, and laboratory glassware. Hot air is a poor conductor of heat and has poor penetrating capacity. Dry-sterilization must be carried at 160°-180°C for 60-90 minutes.

FILTRATION

Filtration through several different types of filters including the modern membrane filters (Millipore filters) is an efficient way of removing larger particles and bacteria from liquids that cannot be treated by other means e.g. human serum albumin. It must be remembered, however, that this may not be exactly equivalent to sterilization as viruses, especially the smaller ones, may pass through such filters.

RADIATION

Radiations used for sterilization fall into two groups non-ionizing and ionizing.

Non-ionizing Radiation: Two types of non-ionizing radiation, infra-red and ultra-violet, are used for sterilization.

Infra-red radiation is another form of dry heat sterilization. It is a convenient method of sterilizing a large number of syringes, sealed in metal containers, within a comparatively short space of time.

Ultra-violet radiation is absorbed by the proteins and nucleic acids and kills micro-organisms by the chemical reactions it sets up in the bacterial cell. It has low penetrating capacity and its main application is to reduce the bacteria in air, water and on contaminated surfaces. All forms of bacteria and viruses are vulnerable to ultra-violet rays below 3000 Å. Excessive exposure of the skin can produce serious burns. Care must be taken to protect the eyes while using ultraviolet radiation for sterilization.

Ionizing Radiation: The lethal action of ionizing radiation is believed to be due to its effect on the DNA of the nucleus and other vital cell components. There is no appreciable rise in temperature. High energy (1.3 MeV) **gamma rays** from cobalt-60 are used to deliver a dose of about 2.5 megarads to sterilize such material as syringes, swabs, culture plates, catheters in bulk and various types of plastic material including disposable plastic heart-lung machines. Unfortunately, glassware tends to develop a brown discolouration on gamma ray sterilization.

ACIDS

(a) **Inorganic acids:**

BORIC ACID: Boric acid and its sodium salt, sodium borate (Borax) are weak bacteriostatic and fungistatic agents. Boric acid is soluble in water upto 5 per cent. This concentration, however, inhibits phagocytosis. Locally, boric acid is not an irritant but when employed repeatedly, it may give rise to cumulative toxicity. Acute boric acid poisoning causes nausea, vomiting, diarrhoea and erythematous rash with depression of circulation, subnormal temperature, profound shock and coma; in some cases, meningeal irritation and convulsions may occur. Chronic toxic effects include stomatitis, eczema and localised edema.

Aqueous solutions of boric acid (2.4%) are used as mouth washes, eye and skin lotions. Mixed with starch, talc or zinc oxide it is used as a dusting powder. Boric acid lotion is sometimes used as washes for the bladder and vagina.

Boric acid I.P. is a white crystalline powder, with a slightly acid and bitter taste and a sweetish after-taste.

Preparations: (i) Boric talc dusting powder N.F. contains 2.3 g. of boric acid, 5 g. of starch and 50 g. of sterilized, purified talc.

(ii) Boric acid ear drops N.F. contain 0.3 g. of boric acid with 3 ml. of denatured spirit dissolved in 15 ml. of purified water.

(iii) Boric acid eye lotion N.F. contains 3.4 g. of boric acid dissolved in 100 ml. of freshly boiled and cooled purified water.

(iv) Boric acid glycerine: This contains 31 per cent w/v of boric acid.

(v) Borax glycerine I.P.: This contains 12 per cent w/v of borax with glycerin and is used for painting throat and tongue in children.

CHROMIC ACID: This compound, which possesses powerful astringent and germicidal activities is highly irritant. It is commonly used to clean laboratory glassware.

(b) **Organic acids:**

BENZOIC ACID: This organic acid has antibacterial and antifungal properties; in a concentration of 0.1 per cent, it is used as a preservative. The antimicrobial activity of the drug is decreased if the pH of the medium exceeds 5. When taken by mouth, benzoic acid is conjugated with glycine in the liver to form hippuric acid which is excreted in the urine. The drug, therefore, was formerly used as a urinary antiseptic, usually in the form of one of its salts. Benzoic acid is also used to test the liver function. A normal individual excretes 2.5 to 3.5 g. of hippuric acid in urine within 3 to 4 hours when given 5 g. of benzoic acid by mouth. The use of benzoic acid in fungal infection is discussed later.

SALICYLIC ACID: This drug has bacteriostatic, fungicidal and keratolytic properties. It is applied externally in dusting powders, lotions and ointments for the treatment of chronic ulcers, dandruff and parasitic skin diseases. Externally, it produces a slow and painless destruction of the epithelium and it is applied in the form of a paint in a collodion base or a plaster for the destruction of warts and corns. The agent has antifermentative and antiputrefactive properties, but because of its potential toxicity, its use as a preservative is prohibited.

Preparations:

(i) Salicylic acid ointment I.P. contains 2 per cent of salicylic acid.

(ii) Whitfield's ointment: See fungicidal agents.

(iii) Salicylic acid compound dusting powder N.F. contains 1.5 g. of salicylic acid and 2.5 g. of boric acid, made up to 50 g. with sterilised, purified talc.

(iv) Salicylic acid ear drops N.F. contain 0.12 g. of salicylic acid with 8 ml. of glycerin and 15 ml. of specially denatured spirit.

(v) Salicylic acid collodion N. F. contains 12 g. of salicylic acid in 100 ml. of flexible collodion I.P.

(vi) Zinc oxide and salicylic acid paste (Lassar's paste) N.F. contains 6 g. each of zinc oxide and starch with 0.5 g. of salicylic acid and 12.3 g. of white soft paraffin.

MANDELIC ACID: See Chapter 46.

NALIDIXIC ACID: See Chapter 40.

ALKALIES

Alkalies like sodium hydroxide and potassium hydroxide dissociate to produce hydroxyl ions and serve as germicidal agents. They are highly irritant. They are particularly effective against the vegetative forms of Gram-negative organisms and against viruses. They are used for disinfecting excreta from patients with poliomyelitis. In addition, both these alkalies are caustic and may be used for removal of warts.

ALCOHOLS

ETHANOL: The pharmacology of ethyl alcohol is discussed elsewhere in detail. Ethyl alcohol is employed in the concentration of 70 per cent as antiseptic. It, however, exhibits poor activity against bacterial spores and viruses. It is also used for sterilization of surgical instruments although this practice does not destroy the spores and hence, is dangerous.

ISOPROPYL ALCOHOL: This is an inflammable secondary alcohol with an unpleasant burning taste. It is about twice as toxic as alcohol. As a germicide, it is slightly more potent than ethyl alcohol and has a marked degreasing action. It is used in the concentration of 68 to 72 per cent v/v, for disinfection of skin and for sterilization of catgut.

ALDEHYDES

FORMALDEHYDE: Formaldehyde, a gas at room temperature, is used as a fumigant or as 34 per cent w/w aqueous solution. The solution, in the concentration of 1:200, is a highly effective disinfectant against several bacteria, viruses and fungi; a higher concentration is necessary to eliminate spores.

Formaldehyde solution is extremely irritant to the mucous membranes and precipitates tissue proteins in high concentration. When applied to the unbroken skin, it hardens the epidermis and may render it tough.

Acute poisoning with the agent is characterised by abdominal pain, vomiting, diarrhoea, vertigo, depression, severe metabolic acidosis and renal failure; convulsions may appear. Treatment of poisoning is symptomatic. The drug also causes allergic reactions.

Uses: Formaldehyde solution (2-5%) can be used for disinfection of surgical gloves and instruments. It does not damage metal or fabrics. A 10 per cent solution is used for disinfection of excreta, sputa and brush bristles. The solution is sometimes used in dentistry as a mummifying agent for residual pulp tissue along with thymol, cresol, glycerin and zinc oxide in the form of a paste. It is also used with equal parts of cresol or creosote as a dressing for septic root canals. A 3 per cent solution is available for removal of warts on the palms and soles, and a 20 to 30 per cent solution is employed in the treatment of hyperhidrosis. A 4 per cent solution in saline is a common preservative for pathological specimens.

Gaseous formaldehyde for sterilization is used for those articles which cannot be wetted with solutions or subjected to high temperatures. Formaldehyde is obtained by heating formaldehyde solution or formalin tablets.

GLUTERALDEHYDE (Cidex): Gluteraldehyde is a saturated aldehyde which produces a slightly acid solution in water. Buffering it with sodium bicarbonate to a pH of 7.5 to 8.5 makes it a potent bactericide, sporicide, viricide and fungicide. A rise of pH above 8.5 causes polymerization of gluteraldehyde with loss of activity. It is less irritant than formaldehyde to the eyes and the skin. Unlike formaldehyde, it does not damage lenses and cementing material in endoscopes and is superior to it for sterilizing rubber, plastic and metal appliances. It can also be used to sterilize complicated apparatus like respirators. It is available as a 2% solution which is buffered to a pH of 7.5-8.5 with sodium bicarbonate before use.

METHENAMINE: See Chapter 46.

SURFACTANTS

Surfactants are chemical compounds which lower the surface tension of solutions, usually aqueous ones. They are also termed as *detergents*. They can be classified into:

ANIONIC SURFACTANTS: Soaps belong to this category. Anionic surfactants dissociate in aqueous solutions to form a relatively large and complex anion, which is responsible for the surface tension lowering activity. Soaps are mainly effective against Gram-positive and acid-fast organisms. It is likely, however, that their cleansing action is secondary to emulsification of the lipoidal secretions in which the bacteria are embedded; the microorganisms are subsequently enmeshed in the lather and washed away with rinsing. In general, soft soaps derived by combination of unsaturated fatty acids with potassium hydroxide or sodium hydroxide are more efficient germicidal agents than hard soaps formed by the treatment of saturated fatty acids with sodium or potassium hydroxide. The disadvantages of soaps are their narrow antimicrobial spectrum, their incompatibility with cationic surfactants, their susceptibility to precipitation by hard water and their tendency to cause drying and cracking of the skin.

Preparations:

(i) Soft soap I.P. is made by the interaction of potassium hydroxide or sodium hydroxide, with a suitable vegetable oil or oils or with fatty acids derived therefrom. One part of soft soap in 20 parts of warm water is used as an enema to soften impacted feces. Soap liniment I.P. which is an alcoholic solution of soft soap, camphor and lemon grass oil, is a mild counterirritant, and is used in the treatment of sprains and bruises.

(ii) Sodium lauryl sulfate: This anionic surfactant is superior to soaps in being effective in hard water. It is active in both acidic and alkaline media. It is mainly effective against Gram-positive bacteria and is used in medicated shampoos and as a preoperative skin cleanser in a concentration varying from 6.5 to 41 per cent, usually along with another antiseptic.

(iii) Sodium cetostearyl sulfate: This compound is used for the same purposes as sodium lauryl sulfate.

Other anionic surfactants include dioctyl sodium sulfosuccinate used as a fecal softening agent, and sodium tetradecyl sulfate used as a sclerosing agent for varicose veins. These are discussed elsewhere.

CATIONIC SURFACTANTS: Cationic surfactants dissociate into a large and a relatively complex cation, which is responsible for the surface activity and a smaller inactive anion. The cation usually contains a pentavalent nitrogen atom, which is often present as a quaternary ammonium, pyridinium or piperidinium group. In addition to emulsifying and detergent actions, the cationic surfactants have a marked bactericidal activity against both Gram-positive and Gram-negative organisms; higher concentrations are necessary to clear the latter type. They are, however, relatively ineffective against spores, viruses and fungi.

The mechanism of antibacterial activity of cationic surfactants is not clear. It is postulated that by lowering surface tension, they damage the cell membrane resulting in a leakage of vital cellular metabolites and subsequent bacterial death.

Cationic surfactants are most effective in neutral solution; their bactericidal activity is appreciably reduced in acid media. They are incompatible with anionic surfactants like soaps. A significant quantity of these agents is absorbed by cotton, rubber and porous material resulting in a reduction in their effective concentration. As these agents combine readily with proteins, their activity is greatly reduced in the presence of serum, pus and other organic matter. When applied on skin, they tend to form a film under which bacteria, particularly *Pseudomonas aeruginosa* and *Mycobacterium tuberculosis*, may remain viable.

The solutions of cationic surfactants are generally colourless, odourless, non-irritating and non-toxic in bactericidal concentrations. They are stable on prolonged standing and do not deteriorate on boiling or autoclaving. This group is one of the most favoured of the antiseptics at present.

Preparations:

(i) Benzalkonium chloride: This occurs as a white or yellowish white amorphous powder or as gelatinous pieces. It has an aromatic odour, an exceedingly bitter taste and is highly soluble in water.

A 1 : 1000 solution may be used for the pre-operative disinfection of intact, unbroken skin. For application to mucous membranes, denuded skin and for application to burns and wounds, a 1:2000 solution is preferred. Similar concentration is also employed in obstetrics. An aqueous solution not stronger than 1:20,000 is used for the irrigation of bladder and urethra and a 1:40,000 solution for retention lavage of bladder.

A 1:4,000 solution has been used for storing sterilised surgical instruments, usually along with 0.5 per cent sodium nitrite to retard rusting. A 1:8,000 solution is used for soaking baby napkins to prevent napkin rash.

Polythene and nylon tubings and catheters may be cleansed by perfusing them with 1:1,000 solution to remove air and then immersing them in a solution of the same strength for 24 hours. Instruments and polythene tubes, treated with the drug must be thoroughly washed before use as the cationic surfactants have a deleterious effect on nerve tissue. Rubber articles, because of their ability to adsorb the cationic surfactants, should not be stored in such a fashion. A 1:5,000 to 1:20,000 solution is used as a preservative for eye drops.

Benzalkonium chloride lozenges containing 0.001 ml. of benzalkonium chloride solution and benzalkonium pessaries containing 0.3 mg. of the drug are available for the treatment of pharyngeal and vaginal infections respectively.

(ii) Cetrimide I.P. (Cetavlon): This is a creamy white powder with a bitter and astringent taste, freely soluble in water. A concentration of 0.1 to 1 per cent in water is used for similar purposes as benzalkonium chloride. A 1:20,000 concentration is used as a preservative for eye drops. Cetrimide cream B.P.C. contains 5.0 g of cetrimide, 50.0 g of cetostearyl alcohol and 500 g of liquid paraffin made upto 1000 g with water. Cetrimide lotion contains 1 per cent centrimide in water.

(iii) Miscellaneous: Other cationic surfactants available include cetylpyridinium chloride, dequalinium acetate and triclobisonium chloride.

AMPHOLYTIC SURFACTANTS: Ampholytic surfactants are derivatives of long chain N-substituted amino acids and can have anionic, non-ionic or cationic properties depending on the pH. They are anionic at a pH above their isoelectric point and cationic at a pH below it. They have the detergent properties of anionic surfactants and the antiseptic properties of cationic surfactants. They, however, are incompatible with both anionic and cationic agents. The compounds available for use include sodium N-dodecyl alanate, and dodecyldi-(aminoethyl)-glycine hydrochloride.

POLYSORBATES: The elimination of one molecule of water from the hexahydric alcohol, sorbitol, results in the formation of compounds termed sorbitans, while elimination of another water molecule results in the formation of sorbides. By esterification of these with fatty acids, non-ionic surfactants are produced. These are termed polysorbates. These substances are active water in oil emulsifying agents, while their polyoxyethylene derivatives are non-ionic, oil in water emulsifying agents.

The polysorbates and their polyoxyethylene derivatives such as Tween 80, are widely used in pharmacy in the preparation of cream, ointment and suppository bases and for emulsification of fixed and mineral oils. They may be employed internally to improve the absorption of fat and fat soluble vitamins. They are also used as surface active agents in insecticides and fruit spraying solutions, as industrial detergents and in the manufacture of cosmetic creams. They are devoid of antiseptic activity.

Phenols and related Compounds

PHENOL (Carbolic acid): Phenol, one of the oldest antiseptics, was introduced in medicine in 1867, by Lord Lister. Phenol is a potent bactericidal and fungicidal agent. It probably acts by denaturing the bacterial proteins. It is mainly effective against non-sporulating pathogens. All spores and most viruses are resistant. It rapidly penetrates the skin, the mucous membranes and other tissues and acts as a local anaesthetic and a general protoplasmic poison. Local anaesthesia is preceded by a feeling of warmth and tingling. It is extremely irritating to exposed tissues and may cause necrosis. Reduction in temperature and an increase in pH considerably interfere with the bactericidal effect of phenol. The antiseptic and corrosive properties are greatly reduced if it is dissolved in alcohol, glycerin or fixed oils.

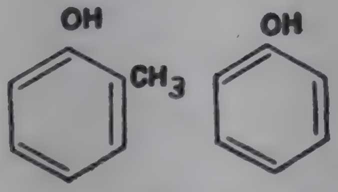


Fig. 56.1: Ortho-cresol Phenol

Phenol is rapidly absorbed on oral administration. It can also penetrate intact, unbroken skin. The drug has no bacteriostatic action in the intestine. Part of the absorbed portion is conjugated and excreted in the urine as benzene sulfonates and glucuronates while a part is excreted unchanged. The degradation products, upon oxidation, impart a greenish tinge to the urine.

Oral ingestion of phenol results in severe gastrointestinal corrosion, pain, vomiting and shock. Collapse occurs within a few minutes, body temperature falls and even convulsions may occur; death is usually due to respiratory failure. Treatment is essentially symptomatic.

Preparations:

(i) Phenol I.P. occurs as pinkish, needle-shaped, deliquescent crystals, sparingly soluble in water but freely soluble in alcohol.

(ii) Phenol glycerin I.P. contains 16.00 per cent w/w of phenol in glycerin.

(iii) Phenol eardrops N.F. contain 5-6 ml. of phenol glycerin I.P. made upto 15 ml. with glycerin.

Uses: Phenol is no longer used as an antiseptic because of availability of better drugs.

A 0.5 per cent solution is occasionally used as antipruritic on the skin and with glycerin, as a mouth wash.

In dentistry, liquefied phenol has been used as an analgesic for sensitive dentine, and with camphor, to allay pain in exposed pulps.

A solution of phenol in glycerin is used in infections of middle and external ear. The agent has been occasionally used as a 5 per cent solution in almond oil for sclerosing haemorrhoids.

Rideal Walker Coefficient (Phenol coefficient): Phenol being one of the oldest antiseptic agents, it was customary to express the antiseptic activity of a new drug in relation to phenol. The index of the comparative activity is known as the *phenol coefficient.*

To determine the phenol coefficient of a new antiseptic, serial dilutions of phenol and the agent under study are made in test tubes and these are inoculated with a known amount of a standard culture of *S. typhi.* The coefficient is the ratio of the minimum bactericidal concentration of phenol to the minimum bactericidal concentration of the new drug. This method, however, tests the antiseptic activity only against a certain bacterial strain. Other factors, modifying the antiseptic activity such as temperature, pH, presence of tissue degradation products etc. are not taken into consideration. Lastly, the use of phenol, as an antiseptic, has declined considerably with the advent of better agents. All these factors have greatly reduced the importance of phenol coefficient.

CRESOL: Cresol is a mixture of the ortho, meta and para methyl derivatives of phenol. In the commercially available product, the meta isomer is the major constituent.

Cresol is nearly 3 to 10 times as active as phenol and yet the toxic potential is nearly equal to that of phenol. It, therefore, has a wider margin of safety. The antiseptic and the systemic actions of the compound are similar to those of phenol.

Cresol I.P. is an almost colourless to pale brownish yellow liquid, becoming darker on keeping or on exposure to light, and with a characteristic phenolic odour. It is sparingly soluble in water and is used as 2 per cent solution.

LYSOL (Cresol with soap solution): This is prepared by saponification of a mixture of cresol with a vegetable oil or the mixed fatty acids, derived therefrom. It contains 50 per cent v/v of cresol. The bactericidal value of lysol varies according to the soap used in its preparation. Soaps made from unsaturated fatty acids exhibit a higher antiseptic activity than those prepared from saturated fatty acids.

Lysol I.P. is a useful disinfectant for hospital and domestic use. It is widely used for disinfection of animal waste products and inanimate objects. Because of its highly irritant nature, it is being replaced by safer preparations like iodophors.

CHLOROXYLENOL (Dettol): It is a less toxic, chlorinated phenol. It is supplied as a 4.8% solution in water. It is effective against Gram-positive and Gram-negative organisms. Surgical dettol used for preoperative preparation of skin contains 1.44 per cent of chloroxylenol; dettol used for disinfection of surgical instruments contains 6.25 per cent of the agent while a 1-3 per cent concentration is employed in the antiseptic cream.

CHLOROCRESOL: This substituted phenol is a potent bactericide with low toxicity; it is more active in acid than in alkaline solution.

Chlorocresol I.P. is sparingly soluble in water. A 0.05 to 0.1 per cent solution is used as a preservative for aqueous injections while a 0.03 to 0.05 per cent strength is employed for preservation of eye drops.

PICRIC ACID: Picric acid or trichlorophenol occurs as bright yellow crystals, sparingly soluble in water but more soluble in alcohol.

Picric acid possesses both antiseptic and local anaesthetic properties. A 1 per cent aqueous solution is employed in the treatment of minor burns and exudative wounds.

Picric acid, when applied over large, denuded surfaces, is absorbed and this leads to systemic toxicity. It is characterised by headache, vomiting, pruritus, stupor and coma. Hepatitis and nephritis may develop in some cases and the skin and mucous membranes are coloured yellow. Treatment is symptomatic.

HEXYLRESORCINOL: This drug, formerly used as an anthelmintic, possesses antiseptic properties and is used in 1:1,000 dilution for this purpose.

BITHIONOL: This is a non-irritant bactericide, particularly effective against Gram-positive cocci, usually employed in soaps and soap solution in a concentration varying from 0.5 to 5 per cent. The drug has also been reported to be effective in the treatment of *Paragonimus westermani* (lungfluke) infestation when given by mouth in the dosage of 50 mg. per kg. in divided portions, on alternate days for a period of 3 to 4 weeks.

THYMOL: Thymol and chlorothymol possess both antiseptic and antifungal properties. Both these, however, are irritating to wounds, have a poor water solubility and lose their bactericidal power considerably in the presence of proteins. They are used in mouth washes and antiseptic solutions. Thymol also has anthelmintic properties.

HEXACHLOROPHANE (G-11): This chlorinated phenol exhibits antibacterial activity against a wide variety of organisms. It is more effective against Gram-positive than Gram-negative organisms. The drug is mainly bacteriostatic and so far, microbial resistance to it has not been reported. The drug retains its activity in the presence of soaps but not so much in the presence of serum or pus. However, the concentration used normally is high enough to compensate for this reduction in activity. It is much less irritant to the skin than phenols although allergic dermatitis can occur.

Hexachlorophane, in the concentration of 1 to 3 per cent, was used commonly as an ingredient of soaps, creams and tooth pastes. Such medicated soaps or tooth pastes do not seem to be superior to non-medicated preparations used for routine purposes. The agent also reduces body odour by preventing the bacterial decomposition of organic material in apocrine sweat, and therefore, is used as a deodorant. Topically it can be used (2-5 per cent) in the treatment of carbuncles, impetigo and seborrhic dermatitis. Topical use may lead to allergic manifestations. The drug can get absorbed from burnt or denuded skin and from mucous membrane and cause neurotoxicity. It can also get absorbed from the unbroken skin in premature infants. Accidental ingestion or the application of high concentrations (6%) to children has caused cardiovascular disturbances, convulsions and respiratory arrest. Hence, it is used locally in a concentration not exceeding 3%.

Hexachlorophane, in the dose of 20 mg. per kg. body weight daily for 3 to 4 days by mouth, has given encouraging results in the treatment of clonorchiasis. The adverse effects include gastrointestinal disturbances and muscular weakness.

CHLORHEXIDINE (Hibitane): This compound acts against a wide range of Gram-positive and Gram-negative organisms. It is non-irritant and is available as 5% aqueous concentrate or 1% water miscible cream. Commercial preparation Savlon contains hibitane and cetrimide.

HALOGENS AND HALOGEN CONTAINING COMPOUNDS

CHLORINE AND CHLORAMINES: Chlorine is one of the most commonly used halogens, largely for purification of water. Chloramines, which release chlorine slowly, are used for disinfection. Chlorine exerts a bactericidal action against a variety of Gram-positive and Gram-negative organisms in a concentration as low as 0.0002 per cent. The acid fast organisms, however, require a much higher concentration. The agent also kills protozoa and viruses.

The bactericidal action of chlorine is significantly reduced in the presence of organic matter.

The antibacterial activity of chlorine is probably due to the formation of hypochlorous acid. An alkaline medium greatly reduces the antiseptic activity of hypochlorous acid by causing dissociation of the acid molecule.

Chlorine poisoning is characterised by severe irritation of the respiratory passage leading to pulmonary edema, and by metabolic acidosis. Treatment consists of administration of oxygen, treatment of shock and venesection to relieve the left ventricular failure.

Preparations:

(i) Chlorinated lime and boric acid solution (Eusol) is prepared by dissolving 1.25 g. of bleaching powder and an equivalent quantity of boric acid in 100 ml. of water. It contains not less than 0.25 per cent w/v of available chlorine. The solution is irritating and should, therefore, be diluted with saline before using on denuded surfaces. It is not recommended for wound irrigation.

(ii) Chloramine: This is an organic

chloride. A 2 per cent solution of the agent is used for irrigation of wounds, while a 0.2 to 0.5 per cent solution is recommended for mouth wash and for irrigation of bladder and urethra. The solution has to be freshly prepared for use.

(iii) Chlorazodin: This agent has been used as a 1:3,300 solution in isotonic buffered saline for irrigating infected wounds.

(iv) Halozone: This preparation, containing 25 per cent of active chlorine, is mainly used for purification of drinking water. Approximately 15 to 20 mg. of the drug achieves a satisfactory disinfection of about 500 ml. of water.

(v) Chlorinated lime I.P. (Bleaching powder) is too irritating to be used on living tissues but is extensively used for purification of water.

IODINE: Iodine is probably the oldest and the most widely used of the antiseptics. It is a powerful bactericidal agent and in addition, also possesses high sporicidal, fungicidal, amoebicidal and a moderate viricidal activity. The germicidal activity of iodine is less influenced than that of chlorine by the pH, the temperature and the time of contact. However, like chlorine, its activity is inhibited by reducing agents and organic material. It is enhanced by alcohol.

Iodine, though employed routinely for treatment of wounds and abrasions, possesses certain disadvantages. Thus, it stains the area of application, is irritating, painful and may delay the healing of wounds. In rare cases, it causes severe reactions, such as fever and generalised skin eruptions. Elemental iodine, if ingested, can cause severe gastrointestinal irritation and shock. Treatment consists of gastric lavage with a solution of soluble starch or 5 per cent sodium thiosulfate, and correction of dehydration and electrolyte imbalance.

Iodism, a syndrome usually seen with prolonged systemic use of iodides, is discussed elsewhere.

Preparations:

(i) Strong iodine solution I.P. (Strong iodine tincture) contains 10 per cent w/v of iodine, 6 per cent w/v of potassium iodide, and 1 per cent v/v of water in 90 per cent alcohol.

(ii) Weak iodine solution I.P. (Iodine tincture) contains 2 per cent w/v of iodine and 2.5 per cent w/v of potassium iodide in 50 per cent alcohol.

(iii) Iodine compound paint N.F. contains 0.31 g. of iodine and 0.62 g. of potassium iodide with mentha oil, water and 90 per cent alcohol in glycerin base. A slightly different composition, containing peppermint oil instead of mentha oil and termed *Mandl's paint* is also available.

(iv) Non-staining iodine ointment N.F. contains 5 per cent iodine with arachis oil and yellow soft paraffin. Methyl salicylate non-staining iodine ointment N.F. contains 5 per cent methyl salicylate in addition.

(v) Aqueous iodine solution (Lugol's solution): Used in thyrotoxicosis. See Chapter 58.

Therapeutic uses: Iodine tincture is usually employed for disinfection of skin prior to surgery. Iodine glycerin preparations are applied to the mucous membranes in the treatment of follicular tonsillitis and pharyngitis. Iodine ointments are used as counter-irritants and have also been used externally as fungicides in the treatment of ringworm.

Iodine is an ingredient of several radio-opaque preparations used for diagnostic procedures such as angiography and pyelography.

The use of iodides as expectorants and in the treatment of thyrotoxicosis is discussed elsewhere. Iodinated hydroxyquinolines are used in the treatment of amoebiasis.

IODOFORM: It is an organic iodide which acts by slowly releasing elemental iodine. The drug, because of its unpleasant odour and poor antiseptic activity, is now rarely used.

IODOPHORS: Iodophors are developed by complexing iodine with surfactants like non-ionic detergents, quaternaries and macromolecules. The detergents act as solubilizers and carriers, combining detergent property with antibacterial activity. Iodophors are non-irritating, non-staining and water-miscible in all dilutions. They owe their germicidal activity to the slowly released elemental iodine. As compared to aqueous or tincture iodine, they are less irritating, less-toxic and non-sensitizing to the skin, though somewhat less effective.

The iodophors available are:

(i) Povidone—iodine: A complex of iodine with polyvinyl pyrrolidone, and

(ii) Undecoylium chloride iodine: A complex of iodine with the cationic surfactant undecoylium chloride.

Iodophors are used for preoperative skin preparation, as local antiseptics, in ringworm and in oral and vaginal moniliasis. Iodophors may also be used for disinfection of operating rooms, wards, nurseries, furniture and equipment.

Oxidizing Agents

HYDROGEN PEROXIDE: This agent, a colourless, odourless liquid, is used mainly as a deodorant and an antiseptic. It owes its action to its ready release of nascent oxygen, when applied to tissues. The application causes an effervescence which mechanically removes the tissue debris from otherwise inaccessible regions. The action, however, is of short duration. Solutions of hydrogen peroxide have poor power of penetration and are comparatively feeble antiseptics. However, they do not combine with tissue proteins. Strong solutions are irritating to the skin.

Hydrogen peroxide solution I.P. contains not less than 6.0 per cent w/v of H_2O_2 corresponding to about 20 times its volume of available oxygen and hence, is described as '20 volume'.

Therapeutic uses: It is used for cleansing wounds, abscesses, for the removal of adhering dressings and for irrigation. It is dangerous to inject hydrogen peroxide into closed body cavities from which the released oxygen has no free exit.

In dentistry, hydrogen peroxide solution is used to clean septic sockets and root canals; diluted with 3 to 8 parts of water, it is a useful deodorant gargle and a mouthwash. It is also used as ear drops.

Other peroxides: These include benzoyl peroxide, magnesium peroxide, urea hydrogen peroxide and zinc peroxide. The last one is used most commonly. It releases nascent oxygen, leaving behind zinc oxide, which has a mild astringent action. It is applied locally as a 40 per cent suspension for disinfecting, deodorising, and promoting healing of burns and other wounds contaminated with anaerobic bacteria. A 25 per cent suspension in water is used as a mouth wash to treat anaerobic infections.

SODIUM PERBORATE: Sodium perborate is a mild antiseptic and deodorant which acts by releasing oxygen upon contact with moisture.

Sodium perborate I.P. is a white, hygroscopic powder, sparingly soluble in water.

POTASSIUM AND ZINC PERMANGANATES: These compounds possess oxidising and astringent properties. Zinc permanganate is more astringent than the potassium salt. The permanganates are caustic as crystals and concentrated solutions. Their ingestion may provoke severe gastrointestinal irritation; potassium permanganate, in addition, causes cardiovascular depression and kidney damage. The insertion of concentrated potassium permanganate preparation into the vagina, for its dubious abortifacient action, causes corrosive burns, ulcerations and severe heamorrhage.

Preparations:

(i) Potassium permanganate I.P. occurs as dark purple crystals, having a metallic lustre. It is sparingly soluble in water.

(ii) Potassium permanganate gargle N.F. contains 25 mg. of potassium permanganate in 100 ml. of water (1 in 4000). It should be freshly prepared.

(iii) Zinc permanganate occurs as brownish-black iridescent deliquescent crystals soluble 1 in 3 parts of water. It is liable to explode spontaneously.

Therapeutic uses: The therapeutic value of potassium permanganate is limited owing to its rapid reduction in the presence of body fluids. It is used as a gargle, mouth wash or for vaginal irrigation; 1 in 10,000 to 1 in 5,000 for urethral irrigation and as wet dressings and in baths for acute dermatoses with a secondary infection. A 1 per cent solution has been used in mycotic infections such as athlete's foot and in poison ivy dermatitis. A 5 per cent solution has a powerful styptic action.

Because of its oxidising property, potassium permanganate as a crystalline insufflation has been employed topically to oxidise snake venom in case of snake bite. A 0.02 per cent solution in water is used for stomach wash in the treatment of alkaloidal poisoning; it, however, does not oxidise cocaine and atropine.

Zinc permanganate, because of its greater astringent activity, is preferred to the potassium salt for urethral irrigation. A concentration of 1 in 4,000 is usually employed.

Potassium permanganate is commonly employed to purify well water.

DYES

Dyes have been used since ancient times in foods, medicines and cosmetics. The natural dyes have now been replaced by the more stable synthetic dyes. These are used as antiseptics, chemotherapeutic, diagnostic and colouring agents. They are non-irritant. The important dyes are:

CRYSTAL VIOLET (Medicinal gentian violet): Crystal violet is a potent antiseptic with a selective action on Gram-positive organisms. Its topical application does not lead to any adverse effect except staining. Given orally, it may cause gastrointestinal disturbances.

Crystal violet I.P. occurs as a dark green powder or greenish glistening pieces having a metallic lustre. It is soluble in water. A 0.5 to 1 per cent aqueous solution is applied topically in the treatment of burns, boils, impetigo, chronic ulcers and mycotic infections of skin and mucous membranes. A compound paint of crystal violet, brilliant green and proflavine has been used in the first aid treatment of burns. Also see Chapter 54.

BRILLIANT GREEN I.P.: This dye, similar in properties to gentian violet, occurs as golden crystals, soluble in water and in alcohol. It is used as a 0.5 or 1 per cent solution in water in the treatment of infected wounds, burns, impetigo and minor injuries.

METHYLENE BLUE I.P.: Methylene blue occurs as a dark greenish, crystalline powder with a metallic lustre. It is hygroscopic and soluble in water. Used in small doses, it has been demonstrated to facilitate the conversion of methemoglobin to haemoglobin. It has, therefore, been used as an antidote in the treatment of cyanide poisoning and drug induced methemoglobinemia. For this purpose, it is given intravenously as a 1 per cent solution in doses of 1 to 4 mg. per kg. bodyweight. It is also used in the treatment of idiopathic methemoglobinemia in the dosage of 300 mg. orally daily along with large amounts of ascorbic acid.

ACRIFLAVINE AND PROFLAVINE: These are acridine dyes effective against many Gram-positive and Gram-negative organisms except *Proteus vulgaris, Pseudomonas aeruginosa* and some strains of *E. coli*. The dyes retain their activity in the presence of body fluids and pus. Proflavine is a more reliable antiseptic than acriflavine and has, therefore, replaced the latter. Acridine dyes stain the site of application; prolonged use may delay the wound healing.

Acriflavine is an orange-red to red

crystalline, odourless powder fairly soluble in water.

Proflavine hemisulfate I.P. has a similar colour but is hygroscopic and much less soluble in water.

The acridine derivatives are used as 1 in 1000 solution for the treatment of infected wounds and burns. A 2 per cent solution in glycerin or pessaries containing 2 per cent of the drug are used in vaginitis and cervicitis.

HEAVY METALS

The pharmacology of heavy metals is discussed elsewhere in detail. Heavy metal salts used exclusively as antiseptics will be discussed here. The salts of heavy metals are capable of destroying the microorganisms in very low concentrations, an action referred to as the *oligodynamic action.* The antiseptic activity is probably due to precipitation of the bacterial proteins.

SILVER COMPOUNDS:

(i) Silver nitrate I.P.: This occurs as colourless or white crystals, extremely soluble in water. Silver nitrate has antiseptic, astringent and caustic properties. If ingested, it produces severe gastrointestinal irritation, vertigo, coma and convulsions. When applied to the skin, it stains the area of application.

The use of aqueous solutions containing 1 per cent of silver nitrate as eye drops in conjunctivitis and ophthalmia neonatorum has now been superseded by penicillin drops. A 1% solution is, however, still used in the treatment of burns.

Silver nitrate stick has been used to remove warts and other small skin growths and for cauterization of wounds and trachoma follicles. The stick should be moistened before use. A 1 in 10,000 concentration is used for irrigation of the bladder and the urethra.

(ii) Colloidal silver compounds: These are ill defined mixtures of metallic silver, silver oxide and various silver proteinates. As silver present in these preparations is largely in the non-ionized form, these compounds do not precipitate tissue proteins. They are non-corrosive, non-irritant and non-astringent. They, however, penetrate the tissues much more readily than the simple silver salts without losing their antibacterial activity.

Prolonged use of silver proteins may result in subcutaneous deposition of silver and subsequent discoloration of the skin, a condition termed argyria.

Mild silver protein I.P. occurs as dark brown scales or granules, freely soluble in water. The silver content varies from 19 to 23 per cent.

Strong silver protein I.P. is a brown somewhat hygroscopic powder, freely soluble in water. The silver content varies from 7.5 to 8.5 per cent. Despite its lower silver content, this preparation is paradoxically termed strong silver protein because it is capable of liberating a higher concentration of silver ions than the mild silver protein, and hence is more powerful and irritating.

Silver proteins are usually applied to various mucous membranes for antiseptic activity. Mild silver protein is employed in a concentration of 5 to 50 per cent. *Argyrol*, a 10 per cent solution of mild silver protein, still enjoys considerable popularity. Strong silver protein is employed in concentrations ranging from 1 to 10 per cent.

MERCURY COMPOUNDS: These probably act by inhibiting the sulfhydryl enzymes of the bacteria. These compounds are irritant, penetrate poorly and are antagonised by proteins. They have feeble action against spores and can cause systemic toxicity. The commonly used inorganic mercurial antiseptics are:

(i) Yellow mercuric oxide: This compound, an orange-yellow, odourless, amorphous powder, insoluble in water, is used in eye ointments for the treatment of blepharitis and conjunctivitis.

Mercuric oxide eye ointment I.P. contains

1 per cent of yellow mercuric oxide.

(ii) Ammoniated mercury: This is a white powder, insoluble in water. It is used locally in the ointment form. It is now rarely used.

Mercuric chloride is now rarely used.

MERCUROCHROME: This organic mercurial compound, which occurs as odourless, greenish, iridescent scales or granules, contains 24 to 27 per cent of mercury. Mercurochrome, though popular, perhaps due to its attractive colour, is relatively a very weak antiseptic. Its action is reduced in the presence of organic matter and has a poor penetrating power. A 1-2 per cent solution of mercurochrome in water is usually employed for treating wounds.

NITROMERSOL: This mercurial compound, a more powerful antiseptic than mercuric chloride, is used as a 1 in 5,000 or 1 in 10,000 aqueous solution for disinfection of skin prior to surgical treatment, for sterilising surgical instruments, for urethral irrigation and in ophthalmology. A 1 in 3,000 eye ointment is employed in conjunctivitis, keratitis, blepharitis and corneal ulcers.

THIOMERSAL: This compound has similar applications as nitromersol. Thiomersal, in the concentration of 0.01 to 0.02 per cent, is also used for preservation of biological products.

Miscellaneous mercurial compounds like phenylmercuric acetate and phenylmercuric nitrate are incorporated in many commercially available spermicidal creams.

ZINC SALTS: Zinc salts possess astringent, corrosive and weak antiseptic properties. The commonly used salts are: (i) Zinc sulfate I.P.: Zinc sulfate occurs as odourless, colourless, efflorescent crystals or as a white crystalline powder. It has an astringent metallic taste and is soluble in water.

Externally, zinc sulfate is used as an astringent lotion for indolent ulcers and to assist granulation. Solutions in the concentration of 0.1 to 1 per cent are sometimes used in angular conjunctivitis and in chronic inflammation of the cornea. The salt is the major ingredient of many commercially available deodorant anidrotics.

(ii) Calamine I.P.: Calamine is a pink powder, almost odourless and tasteless, practically insoluble in water. Chemically, it is basic zinc carbonate (98%) with a small amount of ferric oxide which imparts the pink colour.

Calamine has mild astringent and antiseptic actions and is used as a lotion and a dusting powder in a variety of skin conditions like sunburns, eczema and urticaria, where it also acts as a soothing and protective agent.

Calamine lotion I.P. contains 15 per cent of calamine, 5 per cent each of zinc oxide and glycerine, 3 per cent of bentonite, 0.5 per cent each of liquified phenol and sodium citrate, with rose water as the vehicle. It can also be used as oily lotion or ointment. Watery lotion is usually preferred for treating acute, inflamed, irritable and moist (weeping) lesions; while less acute, drying lesions are better treated by oily lotions or creams.

GASES

Ethylene oxide, formaldehyde and beta-propiolactone in the gaseous form are powerful agents used for sterilization. Properties of formaldehyde has already been discussed. Beta-propiolactone has been reported to have carcinogenic properties and hence has limited usefulness.

ETHYLENE OXIDE: This is a colourless liquid with a boiling point of 10.7°C. At normal room temperatures, it is a highly inflammable and highly explosive gas with a sweet ethereal smell. The explosive tendency can be limited by mixing it with an inert gas such as nitrogen or carbon dioxide and keeping down the concentration of ethylene oxide to 10%. A relative humidity of about 30% is necessary for satisfactory sterilization. It has powerful bactericidal, sporicidal and viricidal properties and a high penetrating capacity. The presence of protein impairs its effectiveness. Its safe use necessitates special equipment which is not commonly available, this is its main drawback. Otherwise, its properties make it an excellent agent for sterilizing complicated equipment like heart-lung machines and respirators as well as suture material. Its explosive nature makes it unsuitable for fumigation of rooms.

Choice of Method of Sterilization: All instruments and apparatus to be sterilized should be first thoroughly cleaned by washing and scrubbing. The same applies to areas for fumigation as the presence of organic matter reduces the efficacy of chemical disinfectants.

Autoclaving is the method of choice for sterilizing all theatre appliances that will withstand it. Those which cannot withstand autoclaving are sterilized by chemical methods: lysol, chloroxylenol or iodophor for surgical blades and scissors; formaldehyde or gluteraldehyde for endoscopes and specialized rubber equipment; and ethylene oxide for heart-lung machines. Syringes are sterilized by boiling, autoclaving, hot air sterlization or gamma radiation. Diabetics are commonly advised to keep their syringe and needle permanently immersed in spirit and to boil them once a week. Gamma radiation is now increasingly used to sterilize many types of disposable articles on a massive scale so that they can be had ready for use. Autogenous and some types of synthetic grafts used in cardiovascular surgery are sterilized with antibiotics.

It is customary to sterilize the air in operation theatres with ultra-violet radiation or with iodophor spray. Ultraviolet radiation is also used to sterilize the air inside sterile dispensing cabinets. Solutions of biological materials such as sera and antibiotics which cannot be sterilized by heat are often 'sterilized' by filtration, though a few vaccines will withstand sterilization by steam at 100°C. Laboratory glassware is ordinarily sterilized in a hot air oven after thorough, preliminary cleansing.

Wards, theatres and sick rooms and the contaminated furniture can be swabbed with formalin or iodophor solutions, fumigated with gaseous formaldehyde or sprayed with iodophor solution. Books and bedding can be fumigated with gaseous formaldehyde or ethylene oxide. Cotton clothing and rubber mattresses can be autoclaved in a hospital. Cotton mattresses, however, cannot be autoclaved and have to be exposed to sunlight and fresh air. If heavily soiled, they are best destroyed by incineration. Incineration is the method of choice for soiled dressings, pathological materials and animal carcasses. If facilities for incineration are not available they are best disinfected with lysol or iodophor. Lysol and iodophor can also be used for disinfecting the excreta of patients with infectious diseases before disposing them into the toilet.

The skin, especially its deeper layers, cannot be sterilized. The best method for reducing the bacterial count on the skin is thorough scrubbing and washing followed by the application of a suitable antiseptic. For pre-operative preparation of the skin, the preferred antiseptics are tincture of iodine (mitis), aqueous iodophor (2%) solution and a 2% solution of hibitane in alcohol (Tinc. Savlon). Alcohol or spirit is commonly applied to the skin before an injection. Acriflavine and chloroxylenol are the popular wound antiseptics though heavily infected wounds are best treated with systemic antibiotics. Although Condy's lotion (a 2% acqueous solution of potassium permanganate) is still the favourite for bladder washes, 1% aqueous solutions of acetic acid and silver nitrate are far more effective for this purpose.

Chloroxylenol is a popular and effective disinfectant for hand-washing by attendants and for sick-room swabbing. Feeding utensils of patients with communicable diseases are best kept separate, washed and finally scalded with boiling water. Soiled bed linen and clothes of patients treated at home should be soaked in a disinfectant such as chloroxylenol and then washed. After recovery of the patient, bed linen and clothes are best laundered and heavy articles such as mattresses exposed to sunlight and fresh air.

Swimming pools and water supplies are generally disinfected by chlorination whereas potassium permanganate is a convenient domestic disinfectant for water, fruits and vegetables.

FUNGICIDES

Drugs used in the treatment of fungal infections can be divided into those used for (a) systemic fungal infections and (b) a local infection.

The antibiotic, amphotericin B, is mainly used for the treatment of systemic fungal infections. Hamycin, another polyene antibiotic, has recently been claimed to be useful against certain systemic fungal infections. These are discussed in Chapter 44.

Antifungal agents used for skin and mucous membrane infections include the antibiotic griseofulvin, nystatin and various other topically applied agents. The characteristic feature of griseofulvin is that, it is administered orally to achieve local effect. Griseofulvin and nystatin are discussed in Chapter 44.

Topically applied antifungal agents are:

BENZOIC ACID AND SALICYLIC ACID: These agents possess antifungal properties. Salicylic acid is a comparatively weak antifungal agent but has keratolytic properties. Benzoic acid compound ointment N.F. (Whitfield's ointment) contains 6 per cent of benzoic acid and 3 per cent of salicylic acid in emulsifying ointment. This is a commonly employed and highly effective preparation. It is mainly used in the treatment of tinea versicolor, tinea pedis and other dermatomycoses.

CHLORPHENESIN: This agent has antibacterial, antifungal and antitrichomonal properties. It is mainly used in the prophylaxis and treatment of dermatophytoses. It is used topically as 0.5 per cent ointment, as a dusting powder or an aerosol containing 1 per cent of the drug. Pessaries containing 1 per cent of the drug are used in the treatment of fungal and trichomonal infections of the vagina.

TOLNAFTATE (Tineaderm): This drug is effective in the treatment of superficial fungal infections of the skin caused by trichophyton and epidermophyton though its superiority over the older antifungal preparations is not established. The drug is not effective against tineasis of nails and hair and relapses are frequent when it is employed in the treatment of tinea rubrum infection. No serious adverse reactions have been reported. It is used as 1 per cent solution or cream, and is nonirritating, nonstaining and odourless.

UNDECYLENIC ACID I.P.: This is a yellow liquid which solidifies on cooling; it has a characteristic odour and is practically insoluble in water.

The drug is applied to the skin in the concentrations of 2 to 15 per cent, sometimes in conjunction with zinc undeconate, in the treatment of dermatophytoses, particularly for tinea pedis. For application to mucous surfaces, however, a concentration exceeding 1 per cent should not be used as it may cause burning. The maximum antifungal activity of the drug is observed in an acidic medium.

Zinc undecylenate is also used locally in 20% concentration.

DITHRANOL I.P. (Anthralin): This is a yellow, odourless powder, insoluble in water. It is a powerful irritant of the skin and the kidney, and should not be applied to the eyes or tender parts of the skin.

The drug is used as a 0.1 to 1 per cent ointment or paste or as a 2 per cent paint in the treatment of psoriasis, ringworm infections and other chronic dermatoses. Since some patients are hypersensitive to this agent, a preliminary test on a patch of skin should be carried out.

A commercial preparation, Derobin, contains dithranol 1.15% with salicylic acid, coal tar and can be used as an antifungal and keratolytic agent.

CHRYSAROBIN: It is an orange-yellow powder obtained from the wood of *Andira aruroba*, a tree indigenous to India and Brazil. It has similar properties as dithranol but is more irritant and stains the skin and clothing.

ICHTHAMMOL I.P. (Ammonium ichthosulfonate): Ichthammol consists of the ammonium salts of the sulfonic acids of an oily substance prepared from the distillate of bituminous schist or shell or from other sources, together with ammonium sulfate and water. It is an almost black, viscid liquid with a strong and a characteristic odour, soluble in water. It is slightly irritant to the skin.

Ichthammol is used as 10 per cent cream and ointment in the treatment of resistant dermatomycoses and other chronic skin diseases.

SELENIUM SULFIDE (Selsun): This drug has been used in the treatment of tinea versicolor, a chronic fungal infection, caused by *Malassezia furfur*. It is also temporarily effective in the treatment of dandruff. It has mild toxicity but possesses unpleasant odour. It is irritant to the eyes. The drug is commonly used as a 2.5% suspension and the preparation is applied once daily and thoroughly rinsed from the body after 10 minutes. This treatment is repeated daily for 4-5 days.

MICONAZOLE (Daktarin, NuFungex): Miconazole nitrate is a synthetic compound, effective topically against dermatophyte infections, candidiasis and gram-positive bacteria. Applied as a 2% cream, twice daily for 3-4 weeks, it is effective in the treatment of fungal skin infections such as *T. cruris* (Jockey itch) and *T. pedis*. It produces prolonged remission and the incidence of recurrence is claimed to be low. The drug is well tolerated and does not stain skin and clothes. It may be used in resistant cases. Miconazole has been used intravenously and intrathecally in the treatment of fungal meningitis due to coccidioides and cryptococci with some beneficial results.

CLOTRIMAZOLE (BAYb 5097): This new synthetic, antimycotic agent, effective against a variety of human pathogenic dermatophytes including *Histoplasma capsulatum, Coccidioides immitis, Cryptococcus neoformans, Sporotrichum schenckii, Candida* and *Aspergilus*, is effective as a systemic antifungal agent on oral administration. It is mainly excreted in urine. The drug, administered orally in the daily dose of 60 mg./kg. body weight, has given encouraging results in systemic candidiasis and aspergillosis. Apart from mild gastric intolerance, no side-effects have been reported. The drug is still under investigation.

Other topical fungicidal agents include tincture iodine, mercurial salts, phenol, oxidising agents e.g. potassium permanganate and dyes like gentian violet. Fungicidal actions of halogenated hydroxyquinolines and nystatin have already been discussed.

It must be emphasized that fungal skin infections and scabies (discussed later) are common among the population from warm and humid climate, particularly in those with unclean habits. Simple personal hygiene and environmental control measures usually suffice to limit the infection and hence, preventive measures such as cleanliness and mass education are far more important than any drug.

PRINCIPLES OF LOCAL TREATMENT OF SKIN LESIONS

As in other areas of medicine, rational therapy in skin disorders depends upon proper diagnosis. Not all skin diseases need urgent treatment. Some, like very localized psoriasis of the elbow are best left alone. In cases where the diagnosis is not immediately obvious, the prescription of a bland local application such as oily cream B.P. (while awaiting specialist opinion) is better than the indiscriminate use of a blunderbuss commercial preparation containing an antibiotic, a glucocorticoid, and antihistamine and perhaps a local anaesthetic, in the hope that 'something will work'. The use of such an irrational 'dermatological potpourri' can so change the morphology of the lesions as to make the subsequent diagnosis difficult, if not impossible.

The next choice is between local and systemic therapy. Whenever such choice exists and both forms of treatment are equally effective, local treatment is always preferable to systemic. However, the local use of some drugs as antihistaminics and (most) antibiotics is best avoided because of the possibility of inducing allergic dermatitis.

Rational external or local treatment of skin diseases exploits physical properties of the compounds used, and hence relies more upon a careful morphologic analysis of skin lesions than the etiologic diagnosis. Local skin therapy, therefore, is modified by the changing patterns of the presenting dermatoses. From the therapeutic viewpoint the skin lesions are divided into (a) oozing and (b) dry types.

(a) An *oozing dermatosis* is associated with dilatation of subepidermal capillaries (erythema), edema and disruption of the epidermis by formation of vesicles. When oozing is copious, folded muslin soaked in a solution such as potassium permanganate (1:5000 or 1:10,000) is applied half-hourly. Evaporation of water produces surface cooling, capillary constriction and reduces oozing. At this stage, a shake lotion (aqueous suspension) such as calamine lotion is substituted and applied every hour. This medicament, in addition to producing surface cooling, forms an adsorbing layer on the lesion. When oozing is very little, calamine lotion is likely to cake, leading to cracking of the skin due to excessive drying. Such lesions are best treated with a liniment or a cream, which produces an emollient effect. Thus, zinc cream is preferred for keeping the skin soft. When oozing ceases but the lesion still appears moist, a paste is applied. It acts as an adsorbing, protective and splinting agent.

Some dermatoses may be associated with infection as indicated by a seropurulent discharge. In such instances an appropriate antimicrobial agent such as iodochlorhydroxyquinoline (Vioform), bacitracin, neomycin or hibitane is incorporated into the preparations described above. Judicious incorporation of a glucocorticoid hastens the subsidence of inflammatory phenomena. The dangers of local corticosteroid therapy are discussed in Chapter 60.

(b) *Dry skin lesions* are best treated with an ointment or a paste. An ointment (generally) promotes percutaneous absorption of the incorporated drug, thus allowing an active pharmacologic effect on the skin.

In cases of urticaria and acne vulgaris, a lotion is generally preferred to other forms of application although the skin lesions are dry. For drug therapy of acne vulgaris see Chapter 44.

(c) When penetration of an active drug through the epidermis into the dermis is desired, the base must be chosen with care. In general, penetration of medicaments is better from an aqueous base than from an oily base. Further, raising the local temperature of the skin as by a polyethylene occlusive dressing enhances penetration of the active drug such as glucocorticoid.

DRUG THERAPY OF SCABIES

Scabies is caused by the itch mite or the *Sarcoptess scabiei* var. *hominis*. The female mite burrows within the superficial layers of the skin to form tortuous channels in which the eggs are deposited. Transmission of the mites occurs by close body contact and by infected clothes. Unhygienic conditions and crowded housing favour the spread of this infection, which is characterised by intense itching, usually worse at night. It is important to note that scabies can give rise to urticarial rash leading to eczematous lesions, which can be mistaken and wrongly treated with local and even oral steroid therapy. The principles of treatment are:

(a) Every member of the household, whether affected or not, must receive the treatment simultaneously.

(b) The medicament is applied to the whole body surface below the neck and this must be emphasized and explained to the patient.

(c) Usually, the drug is applied 3-4 times at the interval of 12 to 24 hours, with bathing and scrubbing of the body before and after the complete course,

(d) Complications are treated either simultaneously or after the basic treatment is over.

(e) Clothings, bed sheets etc. should be disinfected by boiling or by steam, and

(f) Education regarding cleanliness.

Drugs used in the treatment of scabies are:

SULFUR: Both precipitated and sublimated forms of sulfur are used in the treatment of scabies. The scabicidal effect is probably due to its conversion into hydrogen sulfide and parathionic acid. In addition to its use in scabies, sulfur is also employed in the treatment of other chronic skin infections like psoriasis, seborrhoea, ringworm and lupus erythematosus. When taken by mouth, sulfur is converted in the small intestine into alkali sulfides, which by their irritant action, produce a mild laxative effect.

Sulfur ointment I.P. contains 10 per cent (2.5% in children) of sublimated sulfur in a simple ointment base. The ointment is to be rubbed into the skin. Because of its irritant nature, the ointment should not be applied over the face. It stains the clothes. Sulfur, though cheap, needs repeated applications to be effective in the treatment of scabies and the procedure is not very agreeable to the patient.

BENZYL BENZOATE I.P. (Ascabiol): Benzyl benzoate is a clear, colourless, oily liquid, with a burning taste.

Benzyl benzoate is a highly efficient acaricide and is the drug of choice. It is usually applied in the form of emulsion containing 25 per cent w/w of benzyl benzoate. Even after cure of infection, the itching may persist for a few weeks but usually responds to calamine liniment. Children are treated with 12.5 per cent application. Secondary bacterial infection can be successfully treated only after the primary infection is eradicated. The drug is slightly irritant and has an unpleasant smell.

Although effective in pediculosis, benzyl benzoate is not recommended in the treatment of this condition because of its feeble ovicidal activity and relatively short duration of action.

GAMMA BENZENE HEXACHLORIDE (Gammexane): This gamma isomer of hexachlorocyclohexane is an insecticide, larvicide and acaricide. Applied externally, the drug is not so toxic to man or the higher animals; but when ingested, it causes convulsions. The drug is slowly excreted from the body. Other serious but rare toxic manifestation is aplastic anaemia.

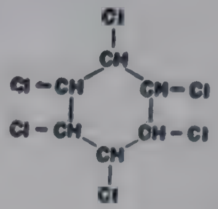


Fig. 56.2: Gamma benzene hexachloride

Gamma benzene hexachloride I.P. is a white, crystalline powder practically insoluble in water.

A 0.1 to 0.5 per cent solution of the agent in kerosene is lethal to flies and mosquitoes. It may be combined with other insecticides, such as pyrethrum extract, to obtain a more rapid lethal effect.

A vanishing cream containing 1 per cent of the drug (Lorexane), applied all over the body in the form of a thin film without preliminary bathing, results in total eradication of scabies. The film is left over for a period of 24 hours following which, the patient is given a bath. An average adult requires 25 g. of the ointment per treatment. Unlike benzyl benzoate and sulfur, the agent is odourless and nonirritant and can, therefore, be applied safely on the face. The treatment may be repeated after a week, if necessary.

It is also useful in pediculosis.

MONOSULPHIRAM (Tetmosol): It is an effective acaricide and is used as 25% solution diluted with 2 to 3 parts of water. It is also incorporated in the soap, recommended for the prophylactic treatment of scabies. The drug may cause mild irritation.

CROTAMITON (Eurax, Crotorax): This is available as 10% lotion or cream. It is applied similarly as sulfur ointment thrice at 24 hour intervals, followed by a bath.

DRUG TREATMENT OF PEDICULOSIS

Pediculosis is still a common condition in tropical countries. It usually affects the scalp (capitis), the body (corporis) and pubic area (pubis). It is responsible for intense itching and may give rise to impetigo and eczematous lesions. Further, during famine and natural calamities, the body louse can act as a vector for typhus, relapsing and trench fevers. Finding of nits or the lice on hair clinches the diagnosis. The drugs usually used are dicophane (DDT), gamma benzene hexachloride (gamma BHC) and kerosene oil.

For pediculosis capitis, 2% DDT application or gamma BHC lotion used as a single application and kept for 24 hours, is adequate. However, usually the treatment is repeated after a week. Gamma BHC is used as 1% cream or 0.2% alcoholic lotion, or 2% cream shampoo; the shampoo is more pleasant to use. However, the application of kerosene, though not very pleasant is the cheapest and equally effective treatment for head lice. It destroys lice and suffocates nits by covering them with an impervious film. Usually, one tablespoonful of kerosene is rubbed into the whole scalp and the head wrapped in a piece of cloth. Two hours later, it is washed thoroughly with soap and water. Kerosene does not cause irritation and usually a single application is all that is necessary.

In patients with pediculosis corporis or pubis, DDT used as 10% dusting powder is highly effective. A single application can give an adequate residual effect against the larvae which hatch out later. Gamma BHC is also equally effective. Occasionally, the lice may show resistance to DDT. Usually, the medicament is applied 3-4 times. The clothing should be disinfected with heat and all the contacts are treated simultaneously.

INSECTICIDES

These drugs, primarily used to destroy insects, are important because of their toxicological properties.

I. **Chlorinated hydrocarbon compounds:** Chlorophenothane, endrin, and gamma benzene hexachloride.

II. **Organophosphorus compounds:** Malathion, parathion, TEPP, and diazinon.

III. **Botanical compounds:** Pyrethrum and rotenone.

CHLOROPHENOTHANE I.P. (Dicophane, D.D.T.): This agent, which occurs as a white crystalline powder or small granules, contains not less than 75.0 per cent of dichloro-diphenyl-trichloroethane. It is practically insoluble in water but slightly soluble in alcohol and kerosene.

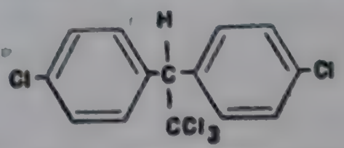


Fig. 56.3: Dicophane (DDT)

DDT is lethal to many arthropods including fleas, body lice, houseflies and mosquitoes. It is a stomach and contact poison i.e. it is absorbed through both the chitinous exoskeleton and the gastrointestinal tract of the insect. It mainly acts by paralysing the central nervous system of the insects.

DDT, because of its low volatility, retains its insecticidal action for a long time. The agent does not have an immediate lethal effect like pyrethrum and rotenone, but these may be combined to advantage with DDT. Its value as an insecticide has, however, diminished considerably due to the development of resistance in many strains of insect species.

DDT is slowly and incompletely absorbed from the gastrointestinal tract of man and other large animals. Although it does not penetrate the intact skin in powder form, when dissolved in the various organic solvents, appreciable percutaneous absorption can occur. Absorption may also occur through accidental inhalation in workers engaged in spraying the insecticide and in animals consuming the fodder dusted with DDT.

Following absorption, large amounts of DDT are stored in body fat depots and in the liver. The drug is excreted unchanged in milk to some extent but most of it is slowly degraded in the tissues and the products eliminated in urine. Poisoning due to consumption of animal milk containing DDT has been reported. DDT stimulates the hepatic microsomal enzyme systems and this may enhance the bio-transformation of drugs like barbiturates.

Acute DDT poisoning is characterised by vomiting, diarrhoea, paraesthesiae, giddiness and fatigue followed by tremors, convulsions and coma; associated solvents like kerosene can cause pulmonary edema. Death occurs from respiratory arrest or from ventricular fibrillation as DDT sensitises the myocardium to adrenaline. The human lethal dose of the insecticide is estimated to be between 10 and 20 g.

Early symptoms of chronic poisoning are loss of appetite, muscular weakness, fine tremors and mental apprehension. Occasionally, anemia, leucocytosis, liver and kidney damage may develop. Recently, it has been shown to produce cancer of the bladder in animals.

Treatment of acute poisoning is symptomatic and includes gastric lavage, saline purgation, administration of short acting barbiturates for the treatment of convulsions, artificial respiration and oxygen. Treatment has to be continued for many days in view of the possible drug storage. Milk, oily substances and sympathomimetic amines should be avoided. Workers engaged in spraying the insecticide should wear protective clothing including face masks.

Uses: DDT is useful for eliminating fleas, bugs, mosquitoes, cockroaches and body lice. For this purpose, a 10 per cent mixture of DDT with a suitable inert diluent like talc is employed. The walls and furniture can be sprayed with a solution of DDT in kerosene; about 100 mg. per square feet usually ensure effective control for about 6 weeks.

DDT is a widely used pesticide in agriculture and in horticulture; usually, a 0.1 to 1 per cent aqueous suspension or a 5 to 10 per cent dust is employed for this purpose.

ENDRIN AND DIELDRIN: These compounds are more toxic than DDT particularly to fish and birds. Endrin is 2 to 3 times more toxic than dieldrin. These agents are employed for residual spraying, usually as 0.6 to 1.2 per cent suspension for similar purpose as DDT.

GAMMA BENZENE HEXACHLORIDE: discussed previously.

Organophosphorus insecticides: The organophosphorus compounds such as malathion are effective against a variety of arthropods like lice, flies and mosquitoes. The compounds are also widely used as agricultural and horticultural pesticides.

The pharmocology of organophosphorus compounds is discussed in Chapter 15.

Botanical compounds:

(a) PYRETHRUM FLOWERS: These are the dried flower heads of *Chrysanthemum cineratiaefolium*. They owe their insecticidal activity to the two esters, pyrethrin I and pyrethrin II.

Pyrethrum flowers are mainly used in the form of an extract and are superior to DDT in being rapidly lethal to the insects. However, even heavy doses have only a brief residual effect. To overcome this drawback, a compound preparation with DDT is usually employed.

Pyrethrum acts mainly by contact and has no appreciable effect on ingestion. It mainly affects the central nervous system of the insect, causing muscular excitation, convulsions and paralysis.

Pyrethrum has relatively low human toxicity. Excessive ingestion, however, may cause initial stimulation of the central nervous system followed by paralysis. The agent also produces contact dermatitis.

Pyrethrum is usually sprayed as solutions containing 0.4 to 0.6 per cent of total pyrethrins. Its applications are similar to those of DDT.

(b) ROTENONE: Rotenone is the principal active insecticidal constituent of *Derris* or *Tuba root.* It is mainly present in the dried rhizome and roots of the Derris plants.

Rotenone is a stomach and contact insecticide. Its action is more rapid but less persistent than that of DDT and less rapid but more persistent than that of the pyrethrum.

Rotenone may rarely cause human toxicity characterised by respiratory stimulation and convulsions. It is used either as a dusting powder diluted with talc or as an insecticidal wash. The latter is of particular value in control of warble fly in cattle.

Cosmetics and Tooth Powders

Various preparations of cosmetic dusting powders contain mainly talc (native magnesium silicate with small amounts of aluminium silicate) which acts as an adsorbent and provides 'slip'. Another substance which also acts as an adsorbent and a mild antiseptic, added to such powders, is zinc stearate, a light, impalpable, amorphous powder. Zinc oxide is commonly used to cover the 'shine', while chalk acts as a colour carrier. Baby powders generally contain zinc stearate and talc in the proportion of 1 to 2. To these basic ingredients, various antiseptics like boric acid, salicylic acid and hexachlorophane (G-11) are added. Application of such powders may cause blocking of the sweat gland pores and hence, after-cleansing is essential. Use of talc on surgical gloves is known to cause granulomatous reaction in wounds. There is no evidence to suggest that medicated cosmetic powders are any better than non-medicated ones for routine use in individuals with healthy skin; on the contrary, medicated powders are costly and liable to produce skin sensitisation.

Tooth powders contain simple chalk as the basic ingredient, with added white soap, saccharin, colour and flavour. Tooth paste, in addition, has water and glycerin. Various antiseptics and chlorophyll which act as deodorant, have been added to these basic ingredients. Evidence suggests that non-medicated tooth pastes are as effective as medicated ones and possess the additional advantage of being cheaper and more acceptable. No toothpaste or powder can, however, act as a substitute for simple and repeated cleansing of mouth immediately after eating.

Most of the commercial cold creams are modifications of a popular emollient preparation, rose water ointment, which contains spermaceti (a waxy substance obtained from the head of the sperm whale), bleached bees wax, almond or prussic oil, rose water and rose oil. Such creams are useful for their soothing and emollient effects.

Anidrotics

Sweating is common in the tropics and no drug should be used to block this normal physiological response. It could, however, become excessive (hyperidrosis) particularly during stress. It is difficult to explain why only some individuals suffer from hyperidrosis. The eccrine sweat glands, although anatomically innervated by sympathetic nerves, are physiologically cholinergic. Anidrotics are the drugs used for controlling hyperidrosis. These can be classified as:

(a) **Systemic anidrotics:** e.g. anticholinergic agents such as belladonna alkaloids and synthetic substitutes like methantheline. These are discussed elsewhere. None of the available systemic anidrotics, however, has a sufficiently predictable action without side-effects.

(b) **Local anidrotics:** e.g. aluminium salts like aluminium chlorhydrate, formalin, glutaraldehyde and esters of hyoscine.

Aluminium chlorhydrate acts by local astringent action and blocks the sweat ducts at the skin surface. Formalin acts by forming keratin plugs in the orifices of sweat ducts; its frequent use may cause allergic reactions. Glutaraldehyde is a tanning agent with antibacterial and deodorant activity. Anticholinergic drugs like propantheline bromide and esters of hyoscine are also effective when applied locally in the form of lotions.

Mild hyperidrosis of the feet is easily managed by foot-baths with potassium permanganate, 1:10,000, and simple talcum powder. Individuals should be instructed to avoid nylon socks and rubber footwear and to use open sandals. Where an emotional factor is suspected, small doses of barbiturates or anti-anxiety agents may help.

Anidrotics, by virtue of their action on sweat secretion, also act as deodorants. However, other drugs which retard the bacterial decomposition of apocrine sweat, may also be used. These include i) chemical deodorants like sodium bicarbonate with 20% talc; aluminium salts; ii) antibacterial drugs like hexachlorophane, tetrachlorosalicylanilide, trichlocarbon, thiram, and bithionol, and iii) perfumes. Some of these agents can cause irritation, allergy, contact dermatitis and photosensitivity reactions. There is no evidence to suggest that chlorophyll, given orally, acts as a deodorant.

It may be noted that there is a great demand for deodorants in today's society and it is estimated that an economically advanced country like the U.S.A. spends about ½ billion dollars a year on being 'nice to be near'. Most of us do not really smell as much as we are made to believe by the advertizers and simple procedures like personal cleanliness, shaving of axillae, washing with ordinary toilet soap and applying, if required, a simple adsorbent like talcum powder will provide similar good results as any expensive spray with much less risk of deodorant dermatitis.

Section XIII: Drugs Used in Endocrine Disorders

57 Anterior Pituitary Hormones

The important functions of self preservation (homeostasis) and species preservation (reproduction) in a multicellular organism demand the highest degree of integration of the various body systems and adaptation to external environment. This integration is brought about by the 'neuroendocrine complex' consisting of the CNS, the ANS and the endocrine glands. These three work in close collaboration with each other and regulate the various vital functions such as circulation, respiration, digestion, excretion and reproduction. The endocrine glands and the ANS serve to carry messages from the highest integrating authority, the CNS, to the body organs and cells. In turn, these also influence the functioning of the CNS.

The endocrine glands consist of groups of highly specialized cells located at various sites in the body. They synthesize and discharge their specialized secretions directly into the circulation without the intervention of a duct (hence the names 'endocrine' and 'ductless' glands). These secretions are called hormones.

What is a hormone? : The word 'hormone' is derived from the Greek word *hormao* which means 'to impel'. It can be defined as a substance secreted by specialized cells and transported to a distance where it exerts its effects upon specific tissues. A hormone may act on other endocrine glands e.g. hypothalamic regulatory (releasing and release inhibiting) hormones, trophic hormones of the anterior pituitary, or may act directly on the tissues e.g. growth hormone, parathyroid hormone, and hormones of the adrenals and gonads. Hormones are secreted by endocrine glands such as the thyroid and the adrenals, and by non-endocrine tissues which secrete gastrin, secretin, pancreozymin and cholecystokinin. Kidneys secrete renin and erythropoietin. 1,25 -Dihydroxycholecalciferol, the most active metabolite of vitamin D synthesized by the kidney, would also appear to qualify as a hormone.

The hormones of the endocrine glands are peptides (hypothalamic regulatory hormones, the anterior pituitary hormones, insulin, glucagon), steroids (adrenal cortical and gonadal hormones), amines (epinephrine and norepinephrine) or derivatives of aminoacids (thyroxine). Generally, a hormone is stored in the same gland which synthesizes it. The hormones of the neurohypophysis, pitressin and oxytocin, are, however, synthesized in the hypothalamus but are stored in the neurohypophysis. The hypothalamic regulatory hormones are synthesized in various areas of the hypothalamus but are stored in the median eminence.

When a hormone acts on another endocrine gland or directly on a tissue, it merely alters the rate of one of the natural functions of that gland or tissue. It does not endow a new function on it. It may either stimulate or depress the function of the latter.

Regulation and release of a hormone: A hormone is directly released into venous blood at a slow basal rate, which in the case of many hormones, shows a natural diurnal rhythm. The present evidence suggests that both hypothalamic 5-hydroxytryptamine (5-HT) and dopamine play important roles in pituitary function and control. Growth hormone, prolactin and ACTH appear to be under direct control by hypothalamic secretion of dopamine or 5-HT while secretion of glycoprotein hormones LH, FSH and TSH is modified by prevailing levels of target gland hormone. Broadly the hypothalamic tryptaminergic pathways predominately stimulate pituitary hormone release, while dopaminergic pathways are predominately inhibitory. There are many factors which either increase or decrease the hormonal secretion:

(1) Various 'releasing' and 'release-inhibiting' hormones of the hypothalamus act on the anterior pituitary to appropriately modify the synthesis and release of the trophic hormones of the latter. They have an intrinsic diurnal rhythm set on them by the brain.

(2) Hormones of the anterior pituitary stimulate synthesis and release of hormones of the target glands, (thyroid, adrenal cortex and gonads). In the absence of these hormones, the target glands not only cease functioning but also undergo atrophy. Hence, these hormones are called *'trophic hormones'*. In turn, increased plasma concentrations of hormones produced by the target glands act on the hypothalamus to reduce the rate of release of regulatory hormones and on the pituitary to reduce its responsiveness to the latter and thus reduce the secretion of the respective trophic hormones of the anterior pituitary (TSH, ACTH, FSH). On the other hand, a fall in the plasma concentration of a target gland hormone leads to a greater release of the corresponding trophic hormone. Thus, in health, any change in the plasma concentration of a target gland hormone tends to correct itself by altering the anterior pituitary function. This mechanism of mutual regulation of hormone activity between two glands is called *"feed-back system"*. It helps to maintain the rates of secretion and plasma concentration of the target gland hormones within a delicately balanced narrow range.

(3) The rate of release of a hormone may also be influenced by changes in the concentration of non-hormonal chemical substances in the plasma. For example, hyperglycemia stimulates the release of insulin from the pancreas but depresses the release of growth hormone from the normal anterior pituitary; hypoglycemia has exactly the opposite effect. A decrease in the level of plasma calcium stimulates the release of parathyroid hormone but depresses that of calcitonin; an increase in the level of plasma calcium has exactly the opposite effect. This is another type of *"feed-back mechanism"* which is also homeostatic in nature.

(4) Increased plasma level of growth hormone is to be found in patients with malnutrition, anorexia nervosa and one variety of dwarfism due to end organ resistance to growth hormone. It is perhaps due to a lack of response of the peripheral tissues to growth hormone. How exactly this increase in growth hormone level is brought about is not clear.

(5) Psychoneurogenic factors can alter the rate of secretion of hormones e.g. anxiety may inhibit gonadotropin secretion; acute stress increases the liberation of catecholamines from the adrenal medulla and corticosteroids from the adrenal cortex.

Role of hypothalamus: Beginning with the pioneering work of Harris at Oxford, it is now well established that the hypothalamus synthesizes and releases several chemical substances which reach the pituitary either along neurones (pitressin and pitocin) or along the portal circulation. Those which are of known chemical structure and are available as synthetic substances are called 'hormones'; others are called 'factors'. As a group, they are called *hypothalamic regulatory hormones*. Pitressin and pitocin have been discussed in detail in Chapters 34, 39. According to current knowledge, there are six 'Releasing Hormones (RH) or Factors (RF)' and three 'Release Inhibiting Hormones (RIH) or Factors (RIF)' produced by the hypothalamus and acting on the anterior pituitary. They are listed in Table 57.1.

Table 57.1: **Hypothalamic Regulatory Hormones**

I. **Releasing hormone (RH) or factor (RF) for:**

- Thyrotrophin (TRH)
- Luteinizing hormone and follicular stimulating hormone (LH/FSH-RH)
- Growth hormone (GH-RF)
- Corticotrophin (CRF)
- Melanocyte stimulating hormone (MSH-RF)
- Prolactin (PRF)

II. **Release inhibiting hormone (RIH) or factor (RIF) for:**

- Growth hormone (GH-RIH)
- Melanocyte stimulating hormone (MSH-RIF)
- Prolactin (PIF)

They are synthesized in the cell bodies of the neurones in different parts of the hypothalamus, travel along the axons of these neurones and are accumulated in their dendrites in the median eminence. In response to appropriate stimuli, they are released into the portal circulation along which they travel to the anterior pituitary to exert their releasing or release-inhibiting actions on the trophic hormones of the latter. The hypothalamic releasing hormones and factors are probably released in nanogramme or smaller quantities. They cause the synthesis and release of much larger, microgramme quantities of trophic hormones. In turn, the trophic hormones cause synthesis and release of still larger, milligramme quantities of target gland hormones. This can then be considered as a 'cascading amplifier' system of greatly multiplying the original hypothalamic signal.

It has been shown that some of the hypothalamic regulatory hormones act not only on the corresponding pituitary trophic hormone but also on others to stimulate or inhibit their release.

The release of the hypothalamic factors is regulated via monoamine neurotransmitter synapses which release dopamine, noradrenaline and serotonin (5-HT). Many drugs (reserpine, chlorpromazine, 1-dopa, amphetamine, imipramine, bromergocriptine etc.) appear to act on the hypothalamus and influence the local monoamine concentration and thus, bring about alterations in the secretion of anterior pituitary hormones. Pharmacological manipulation of hypothalamic function has opened new horizons for treating many hypothalamic-pituitary disorders medically in future.

The hypothalamus can thus be regarded as the highest relay centre which integrates the endocrine and the autonomic nervous systems and ensures a smooth coordination of both these systems by the cerebral cortex. The pituitary can, therefore, no longer be considered as the 'conductor of the endocrine orchestra'.

Transport and metabolism of hormones: The hormones are carried in the plasma partly bound to proteins and partly in the free form. The free form is the active form. The bound form is inactive but probably has a storage function, releasing more free hormone as it is utilized by the body.

The free hormone is metabolized in the body either by chemical degradation to other chemical substances or/and by conjugation with sulfuric and glucuronic acids. The metabolic degradation of hormones occurs in the liver, in the target endocrine glands and in the tissues on which they act. Conjugation to sulfates and glucuronates occurs in the liver. Such metabolic degradation and conjugation generally render the hormone less active or inactive. Occasionally, metabolic transformation (e.g. testosterone to dihydrotestosterone) is necessary to render the hormone biologically active. Conjugation, in addition, makes the hormone water soluble (many hormones such as the steroid hormones are water insoluble in their natural state) and capable of being excreted through the kidneys. The kidney excretes such conjugated hormone and also a trace of the free (i.e. non-protein bound) original hormone from the plasma e.g. free hydrocortisone appears in urine in small amounts.

The responses of body cells to hormones are considerably influenced by genetic as well as environmental factors. Important among these are species, race, age, sex, time of the day, season, temperature, nutrition, presence of disease and prior effect of other hormones.

Mechanism of action: Control of cellular activity is (1) partly internal, by the genetic material in the nucleus; it operates by releasing into the cytoplasm varying amounts of messenger ribonucleic acid (mRNA) which regulates the synthesis of specific proteins including enzymes and (2) partly external, by the neurogenic and hormonal messages. The neurogenic messages act by liberating chemical, neurohumoral transmitters in contact with target cells or by causing liberation of hormones from the endocrine glands. The hormones combine with specific receptor sites on target cells and produce their effects by several mechanisms :

(a) *Alteration in the permeability of the cell wall* e.g. insulin stimulates the entry of glucose and the parathyroid hormone that of calcium ions, from the extracellular space into the cells on which it acts.

(b) *Action on the genetic material in the nuclei* where they cause formation of new messenger RNA and thus a stimulation of specific protein synthesis in the cells. Examples are adrenal glucocorticoids, aldosterone, and estrogens. These steroid hormones first combine with a specific receptor protein in the cytoplasm of the responsive cell; the steroid—receptor combination then acts on the nucleus. Growth hormone probably acts directly on intracytoplasmic ribosomes and stimulates protein synthesis.

(c) *Action on the cyclic AMP*: This hypothesis proposed by Sutherland and his co-workers is thought to explain various hormonal and drug actions. According to this hypothesis, a hormone or a drug binds to a receptor on the cell membrane. In many instances, this receptor appears to be an enzyme or enzyme complex, adenyl cyclase. Adenyl cyclase catalyses the conversion of adenosinetriphosphate (ATP), in the presence of magnesium ions, to adenosine -3'-5' cyclic monophosphate or cyclic AMP. Intracellular formation of the cyclic AMP triggers a sequence of events specific to that cell resulting in specific physiological response to the hormone. The present evidence suggests that adenyl cyclase thus may well act as a receptor for various hormones such as adrenaline, glucagon, ACTH, LH, TSH, parathormone and gastrin and various drugs. Adenyl cyclase is present in a wide variety of animal cells and is usually associated with the cell membrane or with intracellular membrane systems. An enzyme phosphodiesterase biologically inactivates cyclic AMP and thus helps to regulate its intracellular concentration (Fig. 57.1). It is possible that just as some hormones act by raising the intracellular cyclic AMP others may act by decreasing its level. Thus, some alpha-adrenergic effects of noradrenaline have been shown to be mediated by decreasing the intracellular levels of cyclic AMP. The enzyme phosphodiesterase is inhibited by methyl xanthines like caffeine and theophylline and these drugs have been shown to potentiate certain hormonal actions.

It must be pointed out that the understanding of the mechanism of hormone action has just begun and a lot of information is still needed to clarify the various complexities.

THE PITUITARY GLAND

The pituitary gland, present throughout the vertebrate kingdom, has become highly specialized in mammals. Together with the hypothalamus, it forms a neuroendocrine relay station for messages from the brain to the rest of the body.

Description of acromegaly by Pierre Marie in 1886 was the beginning of our understanding of pituitary physiology. This was followed by the work of Cushing, who described the effects of hypophysectomy in dogs (1910) and Simmonds, who described the clinical syndrome of hypopituitarism in man (1930). This has been followed by several important advances in our knowledge about the pituitary function, a recent

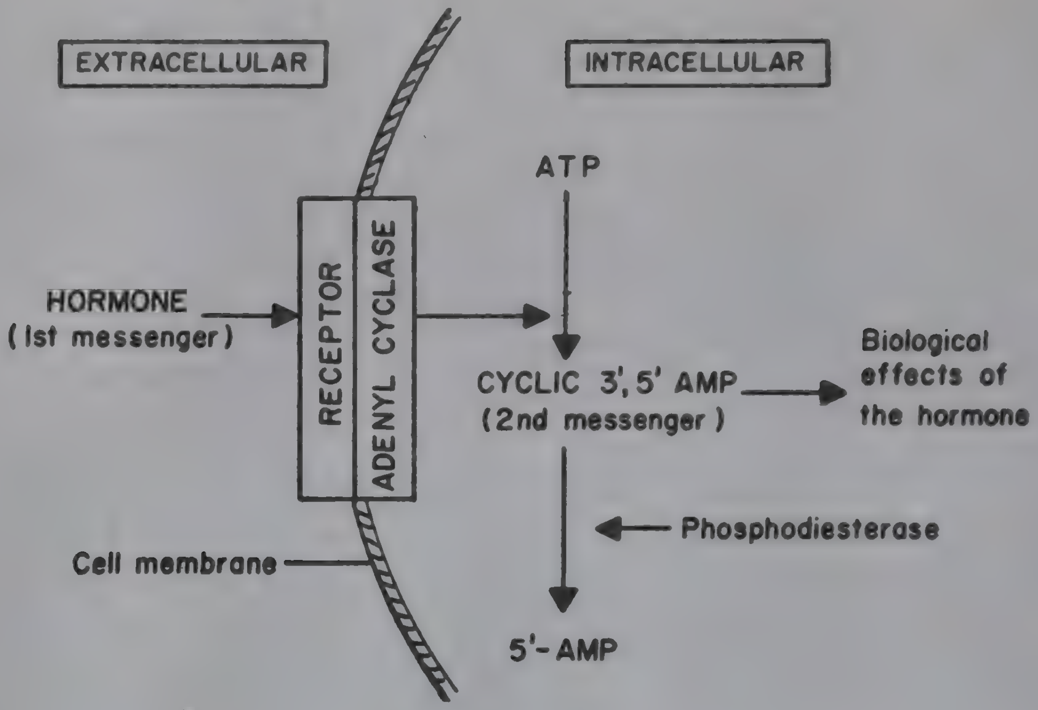


Fig: 57.1: Mechanism of action of certain hormones

example being isolation, purification and therapeutic application of the growth and gonadotropic hormones from the human pituitary gland.

The pituitary gland consists of *adenohypophysis* developed from the oropharynx and *neurohypophysis* developed from the floor of the brain. The former consists of the anterior lobe situated in the sella turcica, the pars tuberalis which spreads on the undersurface of hypothalamus and the pars intermedia which embraces the posterior lobe. The neurohypophysis consists of the posterior lobe of the pituitary and the infundibular stalk which connects it to the hypothalamus.

The pituitary gland has a very rich arterial blood supply and also has a 'portal system' which connects it with the median eminence of the hypothalamus. The latter transmits the hypothalamic regulatory hormones to the pituitary via the portal system. Pituitary gland weighs 0.4 to 1.1 g. in adults and is larger in females than in males.

The anterior lobe of the pituitary contains three types of cells identified on light microscopy: chromophobe, eosinophil and basophil. Several hormones have been isolated from the vertebrate gland. Of these, six have been definitely identified. These are growth hormone (eosinophil cells), ACTH, TSH, FSH, LH (basophil cells) and prolactin (probably basophil cells). The technique of immunofluorescent microscopy has permitted the identification of cells of origin of each of these hormones. Of these hormones, ACTH, MSH and GH are peptides and TSH, LH and FSH are glycoproteins. GH and ACTH have now been synthesized. The melanocyte stimulating hormone (MSH) has been isolated from the pars intermedia of the anterior lobe. Pitressin and oxytocin have been isolated from the neurohypophysis.

The various trophic hormones are described in detail along with the respective target gland hormones elsewhere. The posterior pituitary hormones vasopressin and oxytocin are described in Chapters 33 and 39 respectively.

Effects of hypopituitarism: Manifestations of hypopituitarism depend upon the age of the subject.

(1) **In children:** Retardation of linear growth and of bone age are the two important effects of hypopituitarism in children. These children appear normal at

birth. As they grow, the deviation from normal height becomes more and more marked. They are small but intelligent, delicate and graceful unlike the grotesque hypothyroid dwarfs.

A selective growth hormone deficiency may occur, in which case the diagnosis may be difficult except by the radioimmune assay of plasma growth hormone. When growth hormone deficiency occurs as a part of panhypopituitarism, the associated deficiencies of ACTH and TSH make the clinical diagnosis relatively easier. Panhypopituitarism may be idiopathic or may be due to destruction of the anterior pituitary by a granuloma or a tumour. Isolated growth hormone deficiency is generally idiopathic and often genetic in origin.

(2) **In adults:** Panhypopituitarism may be produced in adults by therapeutic hypophysectomy (as in the treatment of a pituitary tumour, acromegaly, diabetes mellitus or breast cancer), postpartum pituitary necrosis (Sheehan's syndrome) or by destruction by a pituitary tumour.

The clinical manifestations are:

(a) Those due to lack of gonadotropins, such as infertility, impotence, amenorrhoea and total loss of sexual hair;

(b) Those due to deficiency of TSH, giving rise to hypothyroidism, and

(c) Those due to deficiency of ACTH, such as hypotension and fasting hypoglycemia. Pigmentation of Addison's disease is not seen. The severe electrolyte disturbances seen in Addison's disease are not seen as aldosterone production is relatively unaffected.

The patients become moderately plump but obesity is not a feature of this condition; what is more important, cachexia is certainly not seen in these patients. They are relatively well looking and good in colour. Replacement therapy with thyroxine, corticosteroids and sex steroids makes patients essentially normal in all respects except for the infertility.

The clinical manifestations of growth hormone deficiency are not so obvious in adults although a lower fasting blood sugar level, increased lability of blood sugar level and increased insulin sensitivity can be demonstrated.

Damage to the posterior pituitary may produce diabetes insipidus although this is not so severe as that produced by a selective destruction of the posterior pituitary gland.

Effects of hyperpituitarism: Excessive production of anterior pituitary hormones may occur in the presence of demonstrable pituitary disease or in its absence. Such excessive production is associated with gigantism, acromegaly, one form of Cushing's syndrome, the galactorrhoea-amenorrhoea syndrome and rarely hyperthyroidism. Excessive production of the anterior pituitary hormones (TSH, ACTH and Gonadotropins) also occurs in response to failure of function of the respective target glands. High levels of plasma growth hormone have been demonstrated in one form of genetic dwarfism, viz. that due to end organ resistance to growth hormone. In some cases, such excess of pituitary hormone may give rise to important clinical features e.g. pigmentation of Addison's disease, probably due to excess of ACTH.

GROWTH HORMONE: A growth hormone (GH) is found in all vertebrates and even in plants and insects. In addition to its growth promoting properties, it possesses several important metabolic effects which are essential for health but do not appear to be absolutely necessary for survival. It is unique among the anterior pituitary hormones as it acts directly on tissues and not through a target endocrine gland.

Source and chemistry: It is synthesized and stored by the eosinophil cells of the adenohypophysis. It is present in the pituitary gland at all ages and has now been extracted in a relatively pure form from animal as well as human pituitaries. Human growth hormone (HGH) is a polypeptide (Mol. wt. 22000) consisting of a series of 191 amino acids, the sequence of which has now been worked out and the hormone has been synthesized. It is resistant to post-mortem autolysis and to chemical manipulations involved in the extraction. About 5-15 mg. of HGH can be obtained from one anterior pituitary gland.

The growth promoting effect of GH appears to be species specific in that a species responds to GH of homologous origin and to that from higher but not from lower species. The human being responds only to human and simian growth hormones. HGH is also immunologically distinct from GH of non-primate species. It has been proposed but not proved that growth hormone from all the species contains a common 'active core' with additional groupings, and that the ability of a species to respond to a particular GH depends upon its ability to remove these extra groupings and expose the 'active core'.

Plasma levels and regulation of GH secretion: Plasma level of HGH as measured by the radioimmunoassay is less than 3 ng per ml in an adult under basal condition. It rises (as high as 25 ng per ml) several times in spikes during the day, mostly during exercise, during deep sleep (especially in children) and several hours after meals. These spikes are higher in women than in men and can be distinguished from pathological increases in plasma GH levels by their suppression after glucose administration. The plasma HGH levels are extremely high during fetal life and very high during infancy.

Hypoglycemia is the most consistent stimulus to GH secretion. A rapid fall in the blood glucose to less than 50% of the initial level or below 50 mg % represents an adequate stimulus in most subjects. Plasma HGH level also shows a rise during amino acid infusions and after protein ingestion; this response, however, is seen consistently only in females. It is doubtful whether the physiological variations in blood glucose and amino acid levels constitute a potent stimulus to GH secretion. Stress of any kind and vasopressin also stimulate GH secretion. GH responsiveness to insulin hypoglycemia is depressed in obesity, hypopituitarism, hypothyroidism, chronic alcoholism and in individuals on corticosteroid therapy. Therapy with either androgens or estrogens enhances the GH responsiveness both in males and females. Levodopa is a potent stimulus to HGH release.

Spontaneous high plasma levels of GH are found in acromegaly, in anorexia nervosa and in severely malnourished children. They are also found in prediabetic individuals.

The rate of release of growth hormone by the pituitary is regulated by GH-RF and GH-RIH. GH-RIH (somatostatin) is a cyclic tetra-decapeptide which is active in inhibiting GH release in animals. In man, it inhibits the release of GH during insulin hypoglycemia, arginine and 1-dopa administration and exercise. It also rapidly inhibits the release of GH in acromegaly. This has opened interesting therapeutic possibilities which, at present are hampered by its extremely short half life in circulation, thus necessitating a continuous intravenous infusion.

In addition to GH, GH-RIH inhibits the release of TSH and FSH (both during TRH stimulation), of insulin and glucagon (both by a direct action on the pancreas) and of gastrin. The possible physiological significance of these observations is not known.

The rate of secretion of growth hormone is estimated to be around 0.75 to 3 mg per day. A substantial part of this ocurs during the early hours of sleep. The latter is probably important in the anabolic and repair processes of the body.

Pharmacological actions: The metabolic effects of growth hormone are more marked and are demonstrable with smaller dose in animals and humans with deficient anterior pituitary function than in those with intact function. The major effects include DNA replication and RNA synthesis in the liver, muscle, adipose tissue and cartilage. Although the plasma t/2 of

GH is about 20 minutes, its metabolic effects last much longer.

(a) **Growth:** The growth due to GH affects every tissue and organ in the body. It promotes growth without accelerating skeletal or sexual maturation. The increase in body mass (i.e. growth) produced by GH mainly affects the lean body mass and is due to retention of water, nitrogen and minerals but not of fat. In children, it promotes linear bone growth by acting on the epiphyseal cartilage but does not advance epiphyseal fusion. Its action on the epiphyseal cartilage is not direct but is mediated by a substance (Somatomedin) formed by its action on the liver. This is most easily demonstrated in children with hypopituitarism. In most of such children, the effect continues during many (8-10) years of administration of HGH, although a few become refractory after some months. It is noteworthy that HGH injected at intervals of 2-3 days will promote growth, although the metabolic effects produced by it are of short duration. The growth stimulating effect of HGH is more dramatic in younger than in older children with hypopituitarism.

(b) **Protein metabolism:** GH has a strong anabolic action which can, however, be demonstrated only in animals with an intact endocrine pancreatic function. Retention of nitrogen, phosphate and potassium occurs. Blood urea falls and urinary excretion of hydroxyproline rises indicating increase in muscle mass and collagen synthesis. GH stimulates the transport of amino acids into the cells and thus accelerates intracellular protein synthesis.

(c) **Fat metabolism:** The fasting plasma free fatty acid (FFA) level rises on administration of GH. This is due to the lipolytic action of GH on acute administration. Intracellular accumulation of FFA also occurs. In addition, during chronic administration, it inhibits lipogenesis from glucose and acetate. The free fatty acids thus released are utilised by the tissues, thereby diminishing the utilization of glucose. Under physiological conditions in which GH is secreted without concomitant release of catecholamines, such as occurs during sleep, there is little change in plasma fatty acids. GH may, therefore, be of minor importance in lipolysis in man.

(d) **Carbohydrate metabolism:** Effects on carbohydrate metabolism are complex and difficult to explain in terms of a single basic action of GH.

Plasma levels of glucose and insulin are not changed by the sudden diurnal peaks of HGH secretion but after such peaks, the individual becomes more resistant to insulin and glucose tolerance is slightly impaired.

Continued administration of GH to adult dogs results in diabetes mellitus. If GH injections are stopped in the early stages, this diabetes is reversible (idiohypophyseal diabetes); if it is continued for a long time, permanent diabetes develops (metahypophyseal diabetes). Interestingly, GH cannot induce diabetes in growing puppies, and in pregnant and lactating female dogs.

Hypophysectomy can ameliorate experimental diabetes following pancreatectomy as well as certain manifestations of spontaneous human diabetes. However, such individuals tend to develop fasting hypoglycemia, have exaggerated hypoglycemic response to insulin and are unable to rapidly restore blood glucose to normal after hypoglycemia. This latter is primarily the result of inadequate mobilization of neoglucogenic amino-acid precursors, alanine and glutamine, from the muscle. Impaired hepatic neoglucogenesis is less important in this respect.

Administration of HGH to normal humans and to non-diabetic, hypophysectomized individuals does not cause any significant change in plasma glucose or insulin unless large doses of HGH are used. However, it impairs the utilization of a glucose load. Its administration to diabetics who have undergone hypophysectomy for the treatment of retinopathy leads to a rapid aggravation of the diabetic state with ketosis.

The mechanism of production of carbohydrate intolerance by GH is not clear but is probably due to (a) inhibition of phosphorylation of glucose after its entry into the cell and (b) intracellular accumulation of fatty acids which inhibit glucose utilization by the cells.

Plasma growth hormone levels are known to be high in acromegalics, in prediabetics and in early diabetics. Such patients also have high plasma levels of insulin and disturbed sugar tolerance.

(e) **Mineral metabolism:** As mentioned earlier, retention of potassium, sodium and phosphorus occurs with GH. Calcium absorption by the gastro-intestinal tract is increased to such an extent that a net retention of calcium occurs in spite of increased calcium excretion in the urine. During chronic GH administration and in acromegaly, however, osteoporosis is seen. The hypercalciuric action of GH is not seen in the absence of endogenous parathyroid hormone activity.

(f) **Miscellaneous:** GH induces visceromegaly as seen in patients with acromegaly. Rats receiving GH develop a variety of tumours. GH has been incriminated in the pathogenesis of human breast cancer, and hypophysectomy produces amelioration in a proportion of patients with disseminated breast cancer.

Preparations and dosage: Human growth hormone (Crescormon) is available in vials containing 4 I.U. (2 mg) in lyophilized form, to be dissolved in 2 ml of normal saline before use. The usual dose recommended is about 0.5 I.U. (0.25 mg) per kg body weight per week in 3 or 6 divided doses.

Therapeutic uses of HGH: Hypopituitary dwarfism is the most important indication at present for HGH. Administration of as little as 1 mg. daily by injection stimulates rapid linear growth and 5-10 cm. of height may be added during the first year. This rate of growth slows down from the second year onwards. Most patients continue to respond for several years. A few, however, become refractory after some months; in some of these, the refractoriness can be explained on the basis of development of antibodies to HGH. It must be emphasized that the treatment, to be effective, may well be necessary for several years. No adverse effects have been reported during HGH administration. The dose of HGH used in hypopituitary children should be related to their body weights.

Other varieties of dwarfism: In the majority of dwarfed children including those with constitutional short stature, achondroplasia, gonadal dysgenesis and undernutrition, HGH secretion is normal and treatment with HGH is ineffective. The association of growth retardation with emotional deprivation and parental neglect is due to reversible hypopituitarism and it gets corrected following a change in the environment.

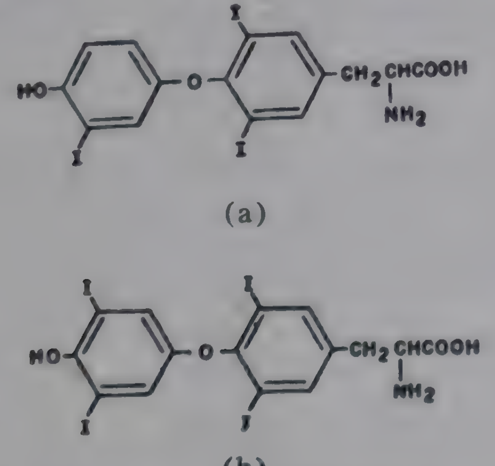
HGH has been shown to be useful in some forms of hypoglycemia (associated with mental retardation) in children.

PLACENTAL GROWTH HORMONE: A substance similar to but not identical with GH has been demonstrated in pregnant human sera, in the placentae and in cord blood. It interferes with a plasma radioimmunoassay of GH during pregnancy.

58 Thyroid and Antithyroidal Drugs

The thyroid gland was discovered by Wharton in 1656. Its function was, however, not known. In 1874, Gull described thyroid hypofunction in man. The results of thyroid ablation experiments were initially misinterpreted because of the simultaneous removal of the parathyroids. In 1895, Magnus Levy reported increased basal metabolic rate (B.M.R.) in patients with hyperthyroidism. The isolation and crystallization of the thyroxine (T_4) was achieved by Kendall in 1915 and its chemical structure was determined by Harrington and Barger in 1926. Tri-iodothyronine (T_3) was detected, isolated and synthesized by Gross and Pitt-Rivers in 1952. The availability of radioactive iodine and the introduction of chromatographic technics in recent years have contributed significantly to a clearer understanding of thyroid physiology.

The thyroid gland acini synthesize two important hormones: thyroxine and tri-iodothyronine. Thyrocalcitonin, secreted by the interstitial cells, is discussed in detail in Chapter 64. Chemically, thyroxine (T_4) is 3, 5, 3', 5' tetra- iodothyronine, and tri-iodothyronine (T_3) is 3, 5, 3' tri-iodothyronine (Fig. 58.1). Substitution of bromine and chlorine for iodine reduces the biological activity of these hormones considerably, while unsubstituted thyronine is inactive. Ether linkage is absolutely necessary for their biological activity and alanine side chain imparts them maximal activity. If the phenolic hydoxyl (OH) group is shifted from position 4', activity of the hormone is either markedly diminished or lost.



(a)

(b)

Fig. 58.1: (a) Tri-iodothyronine (T_3)
(b) Thyroxine (T_4)

Synthesis of thyroid hormones: Sea fish, eggs and milk are good dietary sources of iodide. Dietary iodide is absorbed from the upper gastrointestinal tract and is carried in the plasma as inorganic iodide. The thyroid hormones are synthesized as follows:

(a) *Iodide trapping*: The thyroid traps the plasma iodide circulating through it against a concentration gradient of 25 to 100. This is an active process and is stimulated by TSH. It is competitively inhibited by the thiocyanate and perchlorate ions. The other important organs which compete with thyroid are the kidneys which excrete iodine in urine and to a lesser extent the salivary glands, the gastric and intestinal mucosa, the liver, the placenta and the mammary glands.

(b) *Organic binding of iodine*: The iodide is first oxidized to inorganic iodine in the thyroidal follicular cells with the help of the enzyme peroxidase. Iodine then combines with the amino acid tyrosine in the globulin molecule within the follicular cells to form mono- and di-iodotyrosine (MIT and DIT) successively. These two reactions are extremely rapid but may be defective in certain disease states and are inhibited by thiourea group of antithyroid drugs. The first reaction is also inhibited by sulfonamides, P.A.S. and resorcinol while both reactions are stimulated by pituitary TSH.

(c) *Coupling*: Thyroxine (T_4) is formed by coupling of two molecules of DIT and tri-iodothyronine (T_3) by coupling of one molecule each of MIT and DIT.

The coupling reactions occur while MIT and DIT are bound by peptide bonds within the thyroglobulin molecule. They are oxidative reactions and need peroxidases, probably the same ones involved in oxidation of iodide to iodine. They are inhibited by thioamide drugs.

(d) *Hormonal release*: Thyroglobulin is first taken up by the follicular cells prior to its hydrolysis. Under the influence of TSH, a protease acts on thyroglobulin to release T_4 and T_3 as well as MIT and DIT. MIT and DIT are deiodinated within the thyroid follicular cells and the iodine is re-utilized for iodinating globulin while T_4 and T_3 enter the circulation directly from the follicular cells.

About 90% of the body iodine is in the thyroid gland, mainly as organic iodine. This large thyroidal pool of iodine (5-7 mg) turns over very slowly at the rate of 1% per day.

Plasma iodine: Most of the blood iodine is present in the plasma. The plasma in health contains about 0.2 to 0.4 μg. of inorganic iodide and 4 to 8 μg. of hormonal iodine per 100 ml. The hormonal iodine is made up mostly of T_4, and a small quantity of T_3. T_4 and T_3 circulate in the plasma partly bound to proteins and partly as free hormones. Plasma protein bound iodine (PBI), 4-8 μg. per 100 ml in health, mainly reflects plasma T_4 level. The major binding protein is thyroxine binding globulin (TBG) which accounts for 60% of the binding capacity of the plasma. The level of TBG is influenced by estrogens and rises during pregnancy. T_4 has a higher affinity than T_3 for the hormone-binding protein in serum. The mean concentration of circulating free T_4 is 2.5 ng./100 ml. and of T_3, 0.3 ng./100 ml. The free hormones are physiologically active and the protein bound fractions act as a reserve. In states of iodine deficiency the thyroid economises on iodine by synthesizing T_3 in preference to T_4. A similar situation is also seen in the rare cases of T_3 thyrotoxicosis in whom plasma PBI is normal but plasma T_3 is elevated. The major fraction 80% of the circulating T_3 is formed from T_4 outside the thyroid. Thus T_4 acts not only as a hormone but also as a prohormone. Although the thyroid normally forms more of T_4 than of T_3 there is increasing evidence that T_3 may be at least as important as if not more important than T_4 in determining an individual's hormonal status.

Various circulating iodine containing compounds in man are given in Table 58.1.

Table 58.1: **Iodine containing compounds in normal human serum.**

Name and Abreviation	Concentration (ng/100 ml) Normal range
3, 5, 3′, 5′—Tetraiodothyronine (Thyroxine—T_4)	4000-11000
3, 5, 3′—Triiodothyronine (Liothyronine—T_3)	70-180
3, 3′, 5′—Triiodothyronine (Reverse T_3—rT_3)	25- 80
3, 5—Diiodotyrosine (DIT)	60-430
3—Monoiodotyrosine (MIT)	90-390
3, 5, 3′, 5′—Tetraiodothyroacetic acid (TETRAC)	80-160
Thyroglobulin (TG)	<150-1500
Iodoalbumin (I-ALB)	?

Reverse T_3 (rT_3) is principally a byproduct of T_4 monoiodination in peripheral tissues, though some may be formed by the thyroid gland. Under normal circumstances the origin of serum DIT and MIT is only partly from gland secretion; dietary and other undisclosed sources may contribute significantly to their concentration in serum. Tetraiodothyroacetic acid is probably a metabolic product of T_4. TG present in blood originates from the thyroid gland and its serum concentration rises with thyroid damage, in thyrotoxicosis, in thyroidites and in some cases of metastatic thyroid carcinoma.

Pituitary thyroid relationship: Thyrotropic hormone (TSH), a glycoprotein (with M.W. of 25000) is synthesized and released by the basophil cells of adenohypophysis under stimulation by TRH from the hypothalamus. The circulating T_3 level modulates the response of the pituitary to the TRH. TSH accelerates all the reactions concerned in the synthesis and release of thyroidal hormones. Further, it stimulates thyroid oxygen consumption, glucose assimilation and glucose oxidation. Its action on the thyroid is modulated by the thyroidal organic iodine content (see thyroid autoregulation) and is mediated by adenylcyclase—cyclic AMP mechanism. Repeated administration of TSH in experimental animals increases the weight and vascularity of the thyroid gland. The iodine content of the gland is reduced. Histologically, the height of the acinar epithelium increases and the colloid content decreases. In the absence of adenohypophysis, the thyroid gland undergoes atrophy which is reversible on administration of TSH. The plasma t/2 of TSH is about 1 hour and the daily estimated secretory rate about 170 milli units.

The commercially available TSH, because of its animal origin, induces the formation of antibodies and hence, is not useful therapeutically. Its main use, has been to distinguish primary hypothyroidism (in which it fails to increase the low radioiodine uptake) from hypothyroidism secondary to hypopituitarism (in which it elevates the initially low radioiodine uptake). For this purpose, it has now been largely replaced by the TRH-TSH test.

TSH secretion rises in the presence of low and falls in the presence of increased circulating T_3 levels, respectively. This mutual regulation of secretory activity by the adenohypophysis and the thyroid is called the 'feed-back' system. This negative feed back is believed to occur at the level of the pituitary rather than the hypothalamus. It has been implicated in the pathogenesis of the simple goitre, a non-inflammatory, non-malignant enlargement of the thyroid gland. If, for any reason such as iodine deficiency, ingestion of goitrogens or genetic enzyme deficiency, thyroid hormone synthesis becomes deficient, the tendency of the plasma T_3 level to fall is countered by an increase in TSH secretion. This may lead to goitre formation.

Plasma level of TSH (measured by radioimmunoassay) is undetectable in hypopituitarism and hyperthyroidism and is markedly elevated in primary hypothyroidism. It is also often elevated in persons who have undergone subtotal thyroidectomy or I^{131} treatment for hyperthyroidism but are actually euthyroid at the moment. Although TSH is initially responsible for the development of most forms of nontoxic goitre, plasma levels are elevated only in goitrous patients who are hypothyroid.

TRH: This synthetic substance is chemically a tripeptide of the composition: (pyro) Glu-His-Pro (NH_2) (Fig. 58.2).

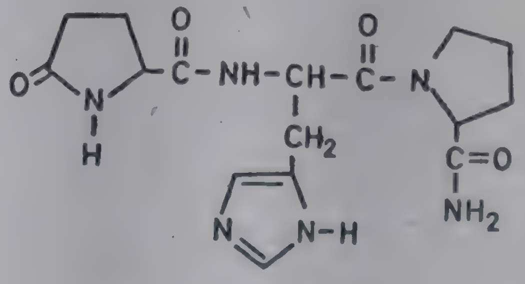


Fig. 58.2: TRH

Human, ovine, bovine and porcine TRH seem to have the same chemical structure. Oral or intravenous administration of TRH results in a rapid rise in plasma TSH level. The plasma TSH response to TRH is blunted in hyperthyroid patients, in euthyroid patients on thyroid hormone therapy and in patients on glucocorticoids. It is excessive in primary hypothyroidism, after thyroidectomy and during therapy with antithyroid drugs. These observations have found diagnostic application in patients with suspected thyroid disorders in the form of a TRH-TSH test.

In addition to TSH, synthetic TRH stimulates the release of prolactin, FSH (in man), LH (in women at luteal peak) and GH (in acromegaly).

Thyroid autoregulation: This term is used to indicate the maintenance of the thyroidal organic iodine stores constant by the thyroid itself, without the mediation of the negative feedback mechanism. An acute increase in the supply of iodide to the thyroid tends to increase its organic iodine content. This is resisted by immediate local inhibition of the iodide trapping mechanism. Further, the thyroid responsiveness to a constant circulating TSH level diminishes in these circumstances. It is likely that this autoregulation is the first, homeostatic, defence mechanism of the thyroid against acute changes in the supply of iodine.

Physiological and pharmacological actions of the thyroid hormones: These have been studied in animals by ablation experiments and by administration of excess of thyroid hormones, and in man, by observing the clinical features of hypo- and hyperthyroid states before, during and after appropriate treatment.

(a) **Calorigenic action:** The thyroid hormones stimulate oxygen consumption and heat production in all tissues except the brain, gonads, lymph nodes, spleen, thymus and dermis. Total thyroidectomy lowers the BMR by 40 per cent while it is markedly elevated in hyperthyroidism. The calorigenic response to externally administered thyroid hormones is most marked in the hypothyroid individual. However, there is a characteristic latent period of several hours or even days between the administration of the hormone and the response.

(b) **Growth:** The thyroid hormones are essential for intra- as well as extra-uterine growth and tissue differentiation. Intra-uterine thyroid deficiency leads to cretinism, the most distinctive feature of which is mental retardation. Deficiency of thyroid hormones appearing after birth leads to severe retardation of physical growth. This is characterized by a marked delay in the bone maturation (retarded bone age). A characteristic epiphyseal dysgenesis, where calcification appears as multiple, small irregular foci causing stippled, porous, fluffy or fragmented appearance in x-rays, is seen. The abnormality occurs in all cartilages which normally should have ossified. It is associated with significant decrease in the serum alkaline phosphatase level. The effects of thyroid deficiency on physical growth are essentially reversible on substitution therapy.

Thyrotoxicosis occurring during childhood leads to a temporary acceleration of linear growth.

(c) **Metabolic actions:** In physiological doses, the thyroid hormones promote growth and protein synthesis and are, therefore, anabolic in their effects. In excessive doses, as in thyrotoxicosis, their effect is catabolic.

The thyroid hormones increase the rate of absorption of glucose from the gut; this action accounts for the lag type of oral glucose tolerance curve which is seen in hyperthyroidism. Peripherally, they increase the rates of cellular entry and intracellular utilization of glucose. Larger doses induce glycogenolysis.

The thyroid hormones enhance the rate of cholesterol synthesis by the liver. They also increase its rate of biliary excretion, its conversion to bile acids and increase its faecal loss. The preponderance of this action over the first one accounts for the elevated levels of serum cholesterol in hypothyroidism. In hyperthyroidism, serum cholesterol is normal unless the individual is malnourished.

They also affect the water and electrolyte metabolism. Thus, the hypothyroid subject retains water and sodium and cannot excrete an added load of water. After starting thyroid medication in such a patient, brisk diuresis and natruresis occur.

(d) **Cardiovascular system:** Thyroxine stimulates the rate as well as the force of contraction of the myocardium. It also increases the cardiac output though this latter effect is probably secondary to peripheral vasodilatation. It acts on the myocardium partly by a direct action and partly by sensitizing it to the effects of catecholamines. Only the latter action is inhibited by beta adrenergic blocking drugs.

(e) **Central nervous system:** Thyroxine is essential for myelination of the CNS. Hence, its deficiency during foetal life leads to an irreversible CNS damage. A variety of neurological changes such as mental retardation, slow tendon reflexes and convulsions are seen in hypothyroidism, while increased irritability, tremors and hyperkinesia are characteristic of hyperthyroidism. Psychoses of various types may also be seen in hypothyroidism.

(f) **Gastrointestinal tract:** Diarrhoea and constipation are seen commonly in hyper- and hypothyroidism respectively. Achlorhydria is more frequent in both these conditions than in the general population. The liver may be depleted of glycogen in hyperthyroidism.

(g) **Reproductive tract and the breast:** Gonadal function is disturbed in males as well as in females in hypothyroidism; menorrhagia is seen in women and infertility in both the sexes. No specific changes are observed in hyperthyroidism. In dairy animals, but not in humans, thyroxine is a potent galactopoietic substance.

(h) **Hemopoietic system:** Anemia, correctable only by thyroid medication, is seen in hypothyroidism. The incidence of megaloblastic anemia is also increased in hypothyroid individuals.

(i) **Skin changes:** Thyroxine deficiency causes deposition of a complex mucopolysaccharide material in the connective tissue of the skin which is responsible for the pallor and roughness of the skin observed in myxedema.

(j) **Miscellaneous actions:** Excess of thyroxine impairs the conversion of creatine to creatinine and also the formation of phosphocreatine, leading to wasteful creatinuria. Various types of myopathies as well as periodic paralysis are seen in hyperthyroidism. Plasma creatine kinase (CPK) level is increased in hypothyroidism and probably indicates muscle dysfunction. Conversion of carotene to vitamin A is defective in thyroid deficiency. While, requirement of both water and fat soluble vitamins appears to be enhanced in thyrotoxicosis.

In some species, these hormones have special functions such as oxygen consumption in fish, metamorphosis in amphibia and plumage growth in birds.

Mechanism of action of thyroid hormones: The exact mechanism of action of the thyroid hormones is not understood. The growth promoting action is explained by the ability of thyroxine to promote protein synthesis in tissues. The GH response of the pituitary to insulin-induced hypoglycemia is blunted in hypothyroidism. It is likely that this action partly explains the growth retardation in hypothyroidism.

The calorigenic effects of physiological doses may also be explained by the same protein-synthesis-stimulating action with resultant formation of intracellular enzymes.

The thyroid hormones also uncouple oxidative phosphorylation, i.e. they decrease the efficiency of production of high energy phosphate bonds in proportion to the rate of prevailing oxidation. Thus, oxygen consumption and heat production are increased but the yield of utilizable energy is relatively decreased. The disruption in the metabolism caused by this action of thyroid hormones can explain the effects of excessive quantities of thyroid hormones as in thyrotoxicosis, but not their basic anabolic and calorigenic actions.

Difference between T_3 and T_4: The overall effects of T_3 and T_4 are qualitatively similar. However, T_3 has a quicker onset of action and is effective in very small doses. Thus, 20 to 25 μg. of T_3 has the same calorigenic effect as 100 μg. of T_4. The onset of action is within 6-8 hours with T_3 and 7-10 days with T_4, even after intravenous administration. After cessation of therapy, the effect lasts for several days with T_4 but wears out quickly after T_3. The elevated TSH levels of hypothyroid patients are suppressed to normal by 0.2 mg. of T_4 daily for 7-21 days or 0.1 mg. of T_3 daily for 3-10 days. In birds, T_4 and T_3 are bound to plasma proteins to the same degree; there is no significant difference in their actions in birds. It is, therefore, likely that the differences between their actions in humans are merely a reflection of the differences in their protein binding and hence in the amounts that enter the cells.

Absorption, fate and excretion: Both thyroxine (40-75%) and triiodothyronine are well absorbed when given orally. Injected labelled thyroxine is concentrated mainly by the liver and the kidney, while T_3 gets distributed to a variety of organs and tissues. These hormones are progressively de-iodinated in the peripheral tissues and iodine thus liberated is returned to the extrathyroidal iodide pool for reutilization. Plasma $t/_2$ of intravenously injected radiothyroxine in health is 6-7 days and that of radio-T_3 is 1-2 days. These are shortened in hyperthyroidism and prolonged in hypothyroidism. Thyroxine appears to be degraded by a stepwise process of deiodination giving rise to T_3 or rT_3. Reverse T_3 is much less potent than T_3 in its calorigenic action. The hormones are conjugated with sulfuric acid in the liver and are excreted in the bile. Oxidative deamination and decarboxylation can also occur. They are partly hydrolysed and reabsorbed in the intestines. About 20-40 per cent of the amount present in the bile is excreted in feces in man.

Adverse reactions: These are similar to the symptomatology of thyrotoxicosis and include diarrhoea, weight loss, palpitation, tremors, hyperkinesia, irritability and occasionally anginal pain.

Preparations and dosage:

(i) Thyroid I.P. is the dried and powdered thyroid gland cleared of connective tissue and fat, obtained from ox, sheep or pig. It is a cream coloured, amorphous powder with a faint meat like odour and taste. It contains not less than 0.085 and not more than 0.115 per cent of iodine and is commonly available as 30 and 60 mg. tablet. Dose: 30 to 240 mg.

(ii) Thyroxine sodium I.P. (Eltroxin) is a white powder without odour and is available commonly as 0.05 and 0.1 mg. tablets. Dose: 0.05 to 0.3 mg. daily.

(iii) Thyroglobulin (Proloid): This consists of the protein from thyroid including the hormone and arginine; it should contain not less than 0.3 per cent organic iodine. It is administered orally in the daily dose of 100 to 150 mg.

(iv) Liothyronine sodium (1-triiodothyronine sodium) is a white or buff coloured, odourless powder almost insoluble in water. It is available as tablets containing 0.005 and 0.025 mg. of the drug and as ampoules containing 0.020 mg. of the dry powder. Dose: 0.005 to 0.1 mg. daily.

The preparation thyroid B.P. or I.P. suffers from certain disadvantages: (i) being a crude preparation it needs biological standardization and (ii) there is a considerable variation from batch to batch in T_4 and T_3 content. Hence, it has now been largely replaced in therapeutics by 1-thyroxine sodium. T_3 is not preferred routinely as its very rapid onset of action is liable to precipitate angina or congestive cardiac failure, especially in the elderly patients with myxedema. Further, the longer half-life of T_4 maintains a substantial peripheral pool of T_4 from which T_3 is slowly formed. This provides a buffer against lapses in treatment. Because of its shorter half-life, T_3 lacks this buffering effect. It is generally reserved for treating myxedema crisis and for carrying out T_3 suppression test.

Combinations of T_4 and T_3 are available for replacement therapy. Claims for their superiority over thyroxine remain unsubstantiated. Further, their theoretical basis is doubtful in view of the current thinking that T_4 acts after peripheral conversion to T_3.

Therapeutic uses of thyroid hormones:

(1) **As substitution therapy:** In *cretinism*, therapy must be started as soon after birth as possible. With proper treatment, normal physical development and linear growth can be achieved. Some degree of mental retardation is, however, inevitable especially in the athyrotic cretins. In cretins with goitres, the thyroid deficiency is milder. Once started, thyroid medication must be continued lifelong. This must be impressed upon the parents. Therapy is started with a small dose which is increased only at fortnightly intervals. The entire daily dose is given once a day. The requirement of thyroxine increases with age: 75 μg. upto 6 months of age, 150 μg at 1-2 years and adult doses from 5 years onwards.

The daily dose is increased to the limit of tolerance as judged by the feeling of well being, pulse rate, irritability and bowel movement. In the infant, adequacy of intellectual development is the crucial guide to adequacy of treatment. In older children, it can be judged by periodic check up for rate of linear growth and bone age, both of which should be restored to normal. Occasionally, while on the optimum thyroxine dosage, the child may become aggressive and quarrelsome; in such cases, the maintenance dose should be reduced.

In *adult hypothyroidism*, a complete reversal of the physical and metabolic abnormalities can generally be achieved by adequate replacement therapy, unless the patient proves intolerant of such therapy. This is likely to happen in patients with coronary heart disease in whom angina may be precipitated or aggravated by thyroxine. For this reason, therapy is always started with a small dose such as 50-100 μg. of thyroxine per day. The daily dose is increased fortnightly by 50 μg. till the patient becomes asymptomatic and well. No attempt should be made to increase the dose beyond this. Adequacy of therapy is best judged clinically and there is no need whatever for repeated determinations of B.M.R. or of plasma T_4 and T_3 levels, at least in the majority of cases. Therapy must be continued lifelong. Before starting the treatment, associated adrenal cortical deficiency, if any, should be corrected, as in such cases, thyroxine, if given alone, may worsen the patient's condition.

(2) **Non-toxic goitres:** Recent studies have demonstrated normal plasma TSH levels in most patients with non-endemic, simple goitres. Hence, the mechanism of action of T_4 in these patients remains obscure. Formerly, it was thought to encourage regression of the goitre by suppressing the plasma TSH level. It may also correct any associated mild hormonal deficiency and act as a source of iodine (100 μg. of levothyroxine sodium contains 57 μg. of iodine). It is used in the dose of 200-300 μg. per day. The goitre shrinks in about 60 per cent of the patients and may completely disappear in 30 per cent. Whether a given patient will respond or not cannot be predicted by any currently available clinical or laboratory parameter. The best responses are, however, seen (a) in the large, diffuse, soft enzyme-deficiency goitres and (b) in the diffuse puberty goitres in patients who have not recently received iodine. In the former group, lifelong treatment is desirable. In the latter group, therapy is continued for 2-3 years but may occasionally have to be given lifelong. Similar dosage is used in the treatment of auto-immune thyroiditis (Hashimoto's disease).

(3) **Hyperthyroidism:** Thyroxine (200-300 μg. per day) administered concurrently prevents the enlargement and increase in vascularity of the diffuse toxic goitre of Grave's disease brought about by anti-thyroid drugs.

(4) **Thyroid carcinoma:** Surgery is the treatment of choice in all cases of thyroid carcinoma. It is followed by radioiodine therapy. Thyroxine has been used after surgery in patients with well differentiated carcinomas as they are believed to be TSH dependent. The dosage is similar to that

used in the treatment of non-toxic goitres. Beneficial effects of thyroxine therapy, however, are as yet unconvincing.

(5) **Thyroid suppression test:** T_4 (300 μg. daily for four weeks) or T_3 (80-100 μg. daily for 5-7 days) is used to differentiate between patients with thyrotoxicosis and those with non-toxic goitres with high uptakes of radioactive iodine. In the latter group of patients, T_4 and T_3 suppress the uptake of I^{131} by 50 per cent or more; in thyrotoxicosis, they do not suppress the uptakes.

(6) **Obesity:** Discussed in Chapter 35.

(7) **As a serum cholesterol lowering agent:** Discussed in Chapter 35.

(8) Thyroxine may occasionally be used as a therapeutic test for hypothyroidism when laboratory investigations are not possible or fail to establish the diagnosis in clinically suspected cases.

(9) Thyroxine is added to the antithyroid drug during pregnancy to minimize its effect on the foetus. However, its value is doubtful because whereas the antithyroid drugs readily cross the placenta to reach the foetus, the thyroid hormones do not cross the placenta. It is also used in the treatment of exophthalmos of thyrotoxicosis. The results, however, are not encouraging.

TREATMENT OF MYXEDEMA COMA

Myxedema coma is the ultimate stage of long standing, untreated hypothyroidism in which mental obtundation and physiological retardation are profound. It is characterised by coma, hypothermia, marked bradycardia and hypotension. It is most likely to occur in elderly people and during cold season. Inadequate treatment, exposure to cold, infection and trauma act as precipitating factors. Alveolar hypoventilation with carbon dioxide narcosis, hypoglycemia, lactic acidosis and dilutional hyponatremia are important associated abnormalities. The diagnosis is essentially clinical but may be confirmed by plasma hormone estimation. Therapy should be started without waiting for the result of the tests.

If available, a large, single parenteral dose (500 μg) of 1-thyroxine sodium is being currently recommended as the best form of treatment. Alternatively, oral T_4 in similar doses or T_3 in smaller doses (50 μg initially, followed by 20 μg every 6-8 hours) may be used. Large doses of a glucocorticoid should be administered parenterally at the same time. Warming should be slow (with blankets) rather than fast. Hypoventilation, if present, should be treated by placing the patient on a respirator and hyponatremia with fluid restriction rather than with hypertonic saline. Fluid and electrolyte balance should be carefully monitored to avoid overhydration. Therapy of myxedema coma remains unsatisfactory and mortality is still high.

IODINE AND THE ENDEMIC GOITRE

Endemic goitre is a manifestation of iodine deficiency. The daily iodine requirement is 1-2 μg. per kg. body weight and can be met with by ingestion of fish 2-3 times a week. Sea-fish, eggs, milk and unpurified common salt obtained from sea water are important dietary sources of iodine. Endemic goitre can be prevented by iodization of the common salt by adding one part of iodine to 10,000 parts of salt. Treatment of an existing simple goitre with iodine is generally unsuccessful. Instead, therapy with thyroxine, as discussed earlier, is more likely to succeed.

ANTITHYROID DRUGS

The clinical manifestations of hyperthyroidism are due to an excess of circulating thyroid hormones. Although the reason for this excess secretion of thyroid hormones is not clear, relief of the hyperthyroid state can be obtained by administration of various drugs. These drugs act by interfering with the synthesis and release of the thyroid hormones.

Drugs which reduce thyroid hormone synthesis (± release) are listed below.

Most of them are used in treating hyperthyroidism. They are:

(I) **Goitrogens:** (a) *Ion inhibitors* such as potassium perchlorate and thiocyanate

(b) *Organic antithyroid drugs*:

(i) Thioamides i.e. thiourea derivatives such as methyl and propyl-thiouracil, methimazole and carbimazole.

(ii) Miscellaneous: Sulfonamides, PAS, amino-glutethimide and resorcinol.

Drugs of group (ii) are not used in the therapy of hyperthyroidism but cause goitre as one of their adverse effects. They probably act by interfering with the oxidation of iodide to iodine in the thyroid gland.

(II) **Iodides**

(III) **Radioactive iodine**

Goitrogens: Experimental goitres were produced by Chesney in rabbits by feeding them with cabbage and by Purves in rats by feeding them with brassica seeds. Potassium thiocyanate was found to produce goitres in some of the hypertensive patients treated with it. Richter's observations on the goitrogenic effects of phenyl thiourea led Astwood and his colleagues to use thioamide drugs in the treatment of hyperthyroidism.

Goitrogens interfere with hormonal synthesis and as the blood level of the hormone falls, increased amount of TSH is secreted by the anterior pituitary. This in turn, stimulates the thyroid which shows hypertrophy, hyperplasia and increase in vascularity. Histologically, the height of the acinar epithelium increases and the colloid decreases.

(a) ION INHIBITORS: Potassium thiocyanate and perchlorate competitively inhibit the trapping of iodide by the thyroid gland. This action is countered by an excess of iodide ions. The thiocyanate is not used in practice because of its potential toxicity. Potassium perchlorate is used in the treatment of hyperthyroidism initially in the dose of 600-800 mg. daily in divided doses. The maintenance dose is 200-400 mg. daily. It is effective in controlling the symptoms of hyperthyroidism and the incidence of toxicity is low. The toxicity includes gastric irritation, fever, skin rashes, lymphadenopathy, agranulocytosis and rarely aplastic anemia. Most patients tolerate the drug very well and it is cheap. It is a useful alternative in patients who are allergic to the thiourea group of drugs. Potassium perchlorate is available as 200 mg. tablets.

Potassium thiocyanate and perchlorate are also used to demonstrate defective organic binding of iodine in the thyroid gland in congenital goitrous cretinism and in Hashimoto's thyroiditis. In these conditions, iodide which is trapped by the gland does not enter the organic binding and hence, is discharged back into the circulation following perchlorate administration. This test is called "the perchlorate discharge test'.

(b) THIOAMIDES: The important drugs belonging to this group are methyl and propyl-thiouracil, methimazole and carbimazole (Fig. 58.3). They have similar modes of action but differ in dosage and in the incidence of adverse reactions.

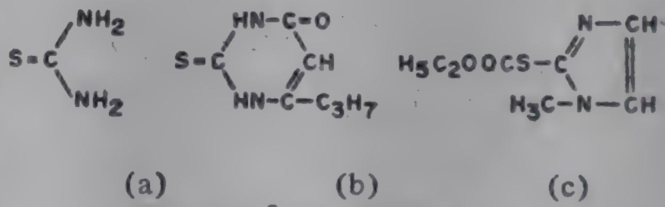


Fig. 58.3:* (a) Thiourea
(b) Prophylthiouracil
(c) Carbimazole

Mechanism of action: These drugs block thyroid hormone synthesis by inhibiting coupling of iodotyrosines, conversion of MIT to DIT and formation of MIT. Trapping of iodide is not affected by them. Moreover, propylthiouracil (but not carbimazole) inhibits the peripheral conversion of T_4 to T_3 and the general metabolic response to T_4 but not to T_3.

Absorption, fate and excretion: These drugs are rapidly absorbed (20-30 minutes) after oral administration. The duration of action of a single oral dose is less than 8 hours. Hence, for effective therapy, they are administered every six to eight hours, round the clock. They are partly metabolized in the body and partly excreted in the urine unchanged. They are also excreted in milk and can cross the placental barrier.

Adverse reactions: The milder adverse effects include drug fever, skin rashes, edema of the feet, arthralgia, lymphadenopathy and hair loss. The more serious effects are leucopenia, agranulocytosis, thrombocytopenia and liver damage. Hypothyroidism is an extension of the pharmacological action of these drugs and is reversible after stoppage of therapy. The incidence of the adverse effects is reasonably small with the drugs in current use and does not probably exceed 5 per cent with most of them.

Preparations and dosage:

(i) Methyl thiouracil, available as 50 mg. tablets. Dose: Initial, 200 to 600 mg. daily; maintenance, 50 to 200 mg. daily.

(ii) Propylthiouracil I.P.: It is commonly available as 50 mg. tablets. Dose: same as methyl thiouracil.

(iii) Methimazole is available as 5 and 10 mg. tablets. Dose: 5 to 20 mg.

(iv) Carbimazole (Neomercazole) is available as 5 mg. tablets; dose: for control, 30 to 60 mg. daily; for maintenance, 5 to 20 mg. daily.

Therapeutic uses:

(1) Treatment of hyperthyroidism: This is discussed later in detail.

(2) Antithyroid drugs were used in past to induce hypothyroidism in certain intractable cardiac conditions. This is no more advocated.

IODIDES: Iodide is the oldest remedy for thyroid disorders including hyperthyroidism. It is the quickest acting drug in hyperthyroidism and its action becomes apparent within 24 hours. The BMR falls at a rate comparable to that seen after subtotal thyroidectomy. The gland becomes less vascular and firm. The acinar cells become smaller in size and the colloid content increases. The gland accumulates organically bound iodine. The maximum clinical benefit is seen within 10-14 days. The hyperthyroid state is, however, only partially controlled by iodide and after a variable period of time, the beneficial effects seem to wear off. With continued treatment, hyperthyroidism may return in its initial intensity or may become even more severe.

Mechanism of action: The exact mechanism of action is not known. It appears to rapidly shut off the release of the thyroid hormones which get stored in the colloid. This effect has been vividly described as 'thyroid constipation'. When given along with a thiourea compound it prevents the increase in the size of the goitre which usually occurs following antithyroid drugs given alone. This is probably related to the decreased responsiveness of an iodine-rich gland to the circulating TSH.

Adverse reactions: Iodism may occasionally occur in a susceptible individual, giving rise to skin rash, rhinorrhea, lacrimation and increased salivation. Iodide causes an escape of thyrotoxicosis if used in a patient on potassium perchlorate. Prolonged use of iodides as in asthma has been reported to occasionally produce a goitre and even myxedema.

Iodides cross the placenta and may cause goitrous cretinism in the foetus. They must, therefore, be avoided during pregnancy. They may precipitate thyrotoxicosis (Jod-Basedow effect) in an occasional patient with a non-toxic goitre. This effect has been occasionally reported even after the use of an iodine containing organic dye as for I.V.P. or aortography.

Preparations and dosage: The two commonly used preparations are sodium or potassium iodide and Lugol's iodine (5 per cent of iodine dissolved in 10 per cent potassium iodide solution). The latter has no special merit except the sanction of tradition. The various commercially available organic iodine preparations are expensive and have nothing to recommend them. The effective dose of sodium or potassium iodide is 6-10 mg. daily and larger doses are not more effective. They can conveniently be used in the form of a saturated solution, 0.3 ml. being given per day or in the form of tablets or capsules.

Therapeutic uses:

(1) They are commonly used in the pre-operative preparation of a patient to reduce the vascularity of the gland. This is the most important use of iodides at present. It is given for 10-14 days pre-operatively *in addition to a thiourea drug*, but must be carefully avoided in patients on potassium perchlorate. Thyroxine given concurrently with antithyroid drugs can obviate the need for the final preoperative addition of iodide to therapy.

(2) Iodides may sometimes be used when it is imperative to control hyperthyroidism very rapidly as in a patient with thyrotoxic crisis or with congestive cardiac failure. For this purpose, they should be given along with a thiourea drug.

Patients with thyrotoxicosis tend to have little hormonal iodine stored in their glands. Iodide administration can increase the hormonal content of the gland. If such a patient is then given a thioamide drug, it fails to act quickly because thioamide blocks synthesis but not release of thyroid hormones. Hence, iodide administration to a thyrotoxic patient should be commenced after first blocking thyroid hormone synthesis with a thioamide drug.

(3) Iodide is used to block the thyroidal uptake before administration of ^{131}I labelled compound such as RIHSA or ^{131}I hipuran.

RADIOACTIVE IODINE: Radioactive iodine, ^{131}I, is concentrated selectively by the thyroid gland. It emits gamma and beta radiations. Gamma radiation is useful for external counting in thyroid function tests. Beta radiation are particles that penetrate only upto 3-5 mm. in the soft tissues. Within this compass, they dissipate their energy to the tissues and act as ionizing radiation. They destroy some of the thyroidal follicles and produce fibrosis. Further, they inhibit the ability of the remaining follicles to replicate.

Preparation and dosage: Radioactive iodine ^{131}I is available as a solution of Na ^{131}I. It is administered orally in the dosage of 5-10 mci. on an empty stomach or after a light breakfast. Patients can be treated on an out-patient basis but are instructed to dispose of their urine carefully into latrine for the next 2-3 days and to avoid close contact with children for a week. Patients are followed up regularly at frequent intervals. The effect of a dose becomes apparent within 3 to 4 weeks and maximum effect is seen within 3-6 months. About 60 per cent of the patients become euthyroid after a single dose. Others may need a second or even a third dose. Decision about the need for a second dose is generally taken at the end of 4-6 months.

Adverse reactions:

(a) **Focal soreness in the neck** as a result of irradiation and an aggravation of the hyperthyroid state are theoretically possible, but are rarely seen.

(b) **Hypothyroidism:** This is the real danger of radioiodine treatment of hyperthyroidism and occurs in 20-30% of the patients in the long run. Hence, treated patients must be followed up carefully, regularly and for long periods. The incidence of hypothyroidism is lower when smaller and more conservative doses are used than with larger doses, but then so is the cure rate of hyperthyroidism.

(c) **Genetic damage:** This possibility cannot be totally excluded at present, but is difficult to demonstrate because the effects are obvious in the later generations.

(d) **Thyroid carcinoma:** Radiation is known to be carcinogenic and the possibility of development of thyroid cancer following radioiodine cannot be totally ruled out, especially if it is used to treat hyperthyroidism in children. Therefore, consensus of the current opinion would reserve radioiodine treatment for adult patients.

(e) **Damage to the foetal thyroid:** The foetal thyroid picks up iodine (and hence radioiodine) from the 16th week onwards. The foetal thyroid is extremely susceptible to radiation and may be quickly destroyed.

Recently, ^{125}I has been used to treat hyperthyroidism in the hope of reducing the incidence of hypothyroidism. It is still under evaluation.

PHARMACOTHERAPY OF HYPERTHYROIDISM

The diagnosis of hyperthyroidism must be established beyond doubt before therapy is started. A large number of *in vitro* and *in vivo* tests are now available for this purpose. Of these, radioiodine tracer test remains the most widely available test in this country. In a typical case, the findings are high early (i.e. two or four hour) radioiodine uptake and high 48 hour plasma protein bound radioiodine level. The latter gives information about the rate of incorporation of iodine into thyroxine; it should be learly distinguished from chemical protein bound iodine which estimates the actual amount of thyroxine present in the plasma.

As the pathogenesis of hyperthyroidism is not known with certainty, the treatment is empirical and is aimed at reducing the production of the thyroid hormones. No drug of practical value is available which directly antagonizes the peripheral tissue actions of the thyroid hormones. TSH was blamed at one stage in the pathogenesis of hyperthyroidism. It is now known that plasma TSH levels are subnormal in this condition and usual feedback mechanism does operate. A specific protein (LATS, or long acting thyroid stimulator) is demonstrable in the plasma of some thyrotoxic patients. It is an antibody to one of the components of the thyroid gland and is capable of directly stimulating the thyroid follicles to secrete more thyroid hormones. Recently, another protein, LATS *protector*, has been incriminated as the culprit in hyperthyroidism.

Hyperthyroidism may be a cyclic disorder and may often undergo spontaneous remissions and exacerbations. In some cases, the exacerbations are specifically related to stressful life situations. Once activated, the disease tends to remain active throughout life in some cases unless definitive treatment (surgery or radioiodine) is given; in others it may undergo remissions spontaneously. Response to drug therapy is variable and cannot be predicted. The aim of the drug treatment is to accelerate the induction of the remission of the thyrotoxic state.

There are three forms of treatment available in therapy of hyperthyroidism. They are (a) antithyroid drugs, (b) radioactive iodine and (c) surgery.

Advantages of thioamide antithyroid drugs: (1) They are well tolerated by most of the patients and are rapidly effective, clinical benefits being apparent in about 2 weeks. The patient is rendered completely euthyroid in about 2-3 months. This euthyroid state can be maintained as long as it is desired by the maintenance doses. If therapy is continued for about 2 years, permanent remission is achieved in about 50 per cent of the treated cases. Thus, surgery with its attendant complications and radioactive iodine therapy with its theoretical hazards can be avoided.

(2) If hypothyroidism occurs, it is reversible on stopping the drug therapy.

(3) They do not generally aggravate the endocrine exophthalmos.

(4) They can be used safely in children in whom surgery and radioiodine are contraindicated. They can also be used during pregnancy.

(5) They can be used to perform a therapeutic test in patients with doubtful diagnosis.

Disadvantages of drug therapy:

(1) Prolonged treatment and follow up are essential. This is difficult in the case of uneducated, unintelligent or uncooperative patients. Furthermore, these drugs are expensive.

(2) In spite of the best efforts, a relapse is liable to occur in 40-50 per cent of the cases. Such patients are liable to relapse after further courses of therapy and hence, need more definitive treatment with radioiodine or surgery.

(3) In certain cases, as those with severe congestive heart failure, their action is too

slow. In such cases, iodides may be used along with a thiourea drug.

(4) They can occasionally cause serious toxicity.

Advantages of radioactive iodine:

(1) The treatment is very convenient, highly effective and can be carried out on an out-patient basis. It can be used with certainty of effects even in unintelligent or uncooperative patients who cannot be depended upon to take their own drugs.

(2) It is pleasant to take without any discomfort or fear and very acceptable to the patient. It avoids surgery and its attendant complications.

(3) There is no fear of relapse once the patient becomes euthyroid.

(4) It is inexpensive as it saves hospitalization required for surgery. In many cases control can be achieved with a single dose.

(5) It can be offered to patients in whom surgery is not possible and to those who refuse surgery, and can be used routinely in all patients past the age of 35-40 years.

Disadvantages of radioiodine: (1) Because of high incidence of hypothyroidism, it cannot be recommended for children.

(2) It is not to be used in patients in the child-bearing age, because of fear of genetic damage due to radiation. It is absolutely contraindicated in pregnancy.

(3) It is a slow acting agent. However, the treatment dose of radioiodine may be followed by a period on antithyroid drugs to achieve early clinical control.

(4) There is a rare possibility of late development of thyroid carcinoma. Thyroid neoplasms, some of them malignant, have been reported in children following ionizing radiation to the neck for conditions like keloid, and eczema and following the treatment of thyrotoxicosis with radioactive iodine.

(5) Since the effects are irreversible, it cannot be used as a therapeutic trial.

(6) Prolonged observation for several years is necessary in order to detect late hypothyroidism in patients who have received radioiodine.

(7) Special facilities for handling the radioactivity are necessary.

Choice of therapy: The treatment of thyrotoxicosis is essentially medical. In most instances, the choice rests between an antithyroid drug and radioiodine.

Antithyroid drugs are indicated in:

(1) children and pregnant women,

(2) young adults with small goitres and comparatively mild thyrotoxicosis of recent onset,

(3) in all patients prior to surgery, and

(4) in conjunction with radioactive iodine, to hasten recovery while awaiting the effects of radiation; for this purpose, they are started 8-10 days after radioactive iodine.

Radioiodine is indicated in:

(1) All patients above the age of 35 years, irrespective of the size and type of goitre and severity of hyperthyroidism.

(2) Recurrence of hyperthyroidism after thyroidectomy.

(3) When associated severe systemic disease contraindicates thyroidectomy and is liable to shorten markedly the life expectancy in younger patients.

Pregnancy is an absolute contraindication to radioiodine. It should also be avoided in children and in young patients who are likely to bear further progeny.

Surgery is indicated in those young adult patients who have (i) failed to respond satisfactorily to drugs or have relapsed after a course of drug therapy, (ii) large, unseemly and especially nodular goitres and (iii) in whom malignancy cannot be entirely ruled out. It should also be advised in an occasional patient who is past 35 or 40 years of age but wishes to have children.

Supportive measures: Sedatives and tranquilizers are helpful in ameliorating the anxiety and overactivity of the hyperthyroid patient. Reserpine and guanethidine were used in past to ameliorate tachycardia and palpitation in these patients.

Propranolol, a beta-adrenergic blocking drug, is useful in controlling the severe tachycardia in these patients. It does not, however, correct the basic metabolic defects of the hyperthyroid state. Hence, using propranolol without antithyroid drugs for preparing these patients for surgery appears irrational and dangerous.

Vitamins and anabolic steroids are also useful when used appropriately in these patients. Congestive cardiac failure should be treated with bed rest and digitalis. Atrial fibrillation should preferably be treated with quinidine in the hope of reversing it to sinus rhythm. Most patients can be allowed to continue work within the limits of their physical tolerance and rest in bed is rarely required in such cases.

TREATMENT OF THYROTOXIC CRISIS

This is a manifestation of extreme hypermetabolism in a thyrotoxic patient and may occur either (a) after thyroidectomy in an improperly prepared patient (surgical storm), (b) in the presence of an infection, injury or any surgical procedure other than thyroidectomy (medical storm). The manifestations are hyperpyrexia, marked tachycardia, extreme irritability and delirium. Nausea, vomiting and diarrhoea may add to the dehydration caused by hyperpyrexia. It is a medical emergency and the treatment must be immediate and aggressive. It consists of:

(1) Treatment of the precipitating cause.

(2) Large doses of an antithyroid drug (propylthiouracil 200 mg. or carbimazole 20 mg. every 4 hours).

(3) Iodide, started a couple of hours *after* the thioamide drug. It may be given intravenously (sodium iodide 1-2 g) or through a nasogastric tube.

(4) Propranolol (iv.) 1.0 mg. repeated every 2 hours, or reserpine 2.5 mg. (IM) every 4-6 hours.

The supportive measures include hydrocortisone 100-300 mg. per day given intravenously, oxygen, adequate intravenous fluids and glucose, large amounts of the B complex group of vitamins and treatment of hyperpyrexia with aspirin, wet packs or ice packs. Congestive heart failure, if present, needs to be treated vigorously with digitalis.

In spite of all this hectic treatment, mortality is still high. The condition, therefore, is best prevented by adequate therapy of every thyrotoxic patient.

59

Insulin and Oral Antidiabetic Drugs

Diabetes mellitus has been known since ages and the sweetness of diabetic urine has been mentioned in Ayurvedic medicine by Sushruta. Its pharmacotherapy, however, is just over 50 years old. The word 'diabetes' (to flow through) was coined by the Greek physician Aeretaeus in the first century A.D. In the 17th century, Willes observed that the urine of diabetics was "wonderfully sweet as if imbued with honey or sugar". The presence or sugar in the urine of diabetics was demonstrated by Dobson in 1755.

In 1889, von Mehring and Minkowski accidentally discovered that pancreatectomized dogs become diabetic in addition to developing digestive disturbances. The non-digestive part of the pancreas, islet cells, was thought to be responsible for the substance which prevented diabetes and this substance was christened 'insulin' by de Mayer (1909), long before its extraction by Banting and Best in 1922. There are few episodes in medical research which are as dramatic as the discovery of insulin, a life saving agent. The chemical structure of insulin was elucidated by Sanger (1960) and the insulin molecule was fully synthesized in the laboratory by 1966.

The major drawback of insulin, is its ineffectiveness when given orally. Hence, the search was continued for an orally effective agent for the treatment of diabetes mellitus. Synthalin A, a biguanide, was the earliest oral hypoglycemic agent to be used in therapy but was found to be too toxic. It is now of historical interest. A chance observation by Janbon (1942) led to the discovery of hypoglycemic action of sulfonamides. This was confirmed by Frank and Fuchs in 1955, who observed the blood sugar lowering action of carbutamide, a sulfonamide, during its trial in infectious diseases. Since then, many sulfonylurea compounds have been introduced as successful oral anti-diabetic agents. In 1957, biguanides staged a comeback into diabetotherapy when Ungar introduced phenformin as an effective and not so toxic oral anti-diabetic drug.

Physiology of carbohydrate metabolism: The main carbohydrates consumed by humans are starch, a polysaccharide, and sugar, a disaccharide.

The ingested carbohydrates are digested successively by

(i) salivary amylase ptylin, which breaks down starch to maltose.

(ii) acid hydrolysis in the stomach,

(iii) pancreatic amylase and maltase and

(iv) lactase, maltase and invertase in the intestinal juices.

Most of the ingested polysaccharides are split to monosaccharides such as glucose, galactose and fructose. They are absorbed mainly in the small intestine, partly by diffusion and partly by active transport. Different sugars are absorbed at different rates, the fastest moving being galactose. Glucose, fructose, galactose and sorbitol are interconvertible in the liver and the main monosaccharide leaving the liver is glucose, which is finally carried by arterial blood to the body cells for utilization.

Utilization of glucose: Tissues differ in their dependence on glucose for their energy needs. Thus, brain utilizes only glucose while most other tissues can utilize glucose as well as fatty acids for their energy requirements. In fact, in times of glucose deprivation, the skeletal and cardiac muscle can derive 90 per cent of their energy from free fatty acids.

A considerable amount of glucose can be utilized by tissues in the absence of insulin, but under these circumstances the blood glucose must rise to much higher concentrations to permit such utilization. Effective insulin action permits the tissues to utilize blood glucose at much lower levels. This phenomenon has been characterized by Butterfield as the 'tissue threshold to glucose', which is normally around 70-90 mg. per cent or higher. Insulin facilitates intracellular entry of glucose and thus conceptually lowers the 'tissue threshold to glucose'.

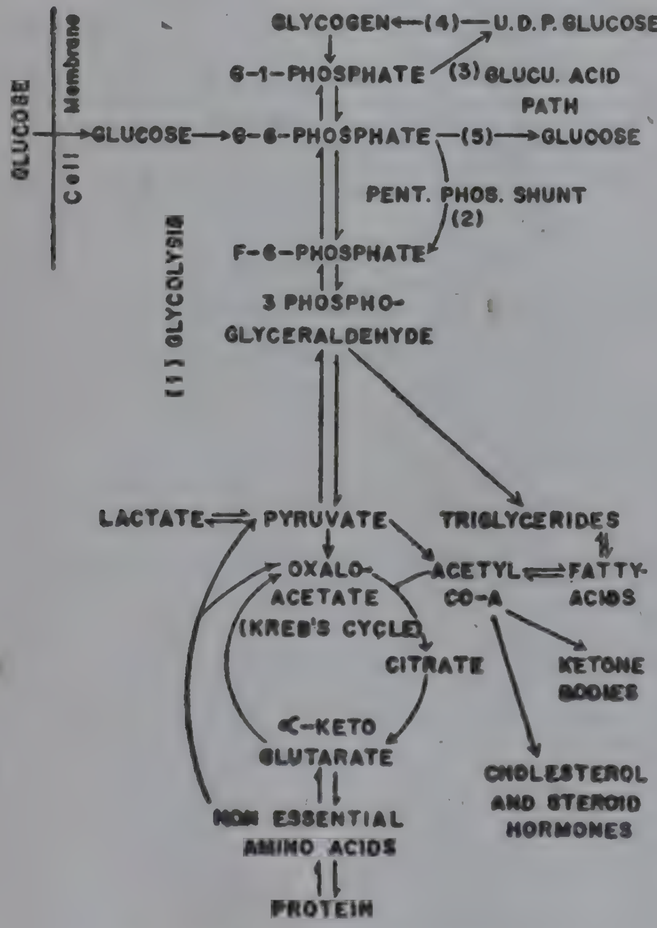


Fig. 59.1: Glucose metabolism.
Numbers in the diagram correspond to the numbers in the text. G=Glucose; F=Fructose.

Immediately on entry into the cell, glucose is phosphorylated with the help of *hexokinase* and enters a series of enzymatic reactions (Fig. 59.1). It is converted to glucose-6-phosphate which is further metabolized in one of the several ways: (1) glycolysis, (2) pentose phosphate pathway, (3) glucuronic acid pathway, (4) glycogenesis and (5) conversion to glucose. *Glucokinase* is a special type of hexokinase present only in the liver.

(1) *Glycolysis* is an anerobic process by which glucose, through successive stages, is converted to pyruvate or lactate. Some of the intermediary steps are shown in figure 59.1. When pyruvate production exceeds the cell oxidation capacity, it is reduced to lactate, this being an anerobic reaction. When plenty of oxygen is available, lactate is converted back to pyruvate. Glycolyis is a relatively inefficient method of energy production and only two moles of ATP are produced for each mole of glucose utilized.

(2) *Pentose-phosphate shunt* is an aerobic multicyclic process that converts a part of glucose-6-phosphate to 3-phosphoglyceraldehyde by a different pathway. This pathway, though quantitatively unimportant, is one of the few sources of TPNH in the body. TPNH is required for lipogenesis and its deficiency contributes significantly to ketoacidosis in diabetes mellitus.

(3) *Glucuronic acid pathway* converts glucose-6-phosphate to uridine diphosphoglucose (UDPG) through G-1-phosphate. UDPG is utilized for synthesis of glycogen and mucopolysaccharides and contributes glucuronic acid required for conjugation of many substances such as bile pigments and steroids.

(4) *Glycogenesis*: Glycogen is derived largely from UDPG by the action of *glycogen synthetase* and to much smaller extent from glucose 1-phosphate by the action of phosphorylase. *Phosphorylase* is mainly responsible for glycogenolysis.

(5) *Conversion to glucose*: Liver and kidney are the only two organs which contain an enzyme *glucose-6 phosphatase* which converts glucose 6-phosphate to glucose. The reaction is irreversible. Muscle cannot convert glycogen to glucose but converts it to lactate which is either utilized locally or goes to liver where it is utilized for neoglucogenesis. The key enzymes in the liver are glucokinase, phosphorylase,

glycogen synthetase, glucose-6 phosphatase and the enzymes concerned with neoglucogenesis.

More than 90 per cent of the energy from glucose is derived from the aerobic oxidation of pyruvate by the tricarboxylic acid cycle (Kreb's cycle). In this cycle, the carbon skeleton of acetyl coenzyme is oxidized to CO_2 and water. The carbon skeleton of oxaloacetate is not oxidized; it is merely regenerated as oxaloacetate after the cycle goes through a full turn. The citric acid formed in this cycle is further metabolised:

(a) with the production of CO_2, DPNH, TPNH and ATP and

(b) with regeneration of oxaloacetate which can carry further acetate (acetyl-coenzyme A) into the cycle.

DPNH produced is required for neoglucogenesis in the liver and TPNH is important for lipogenesis.

Acetylcoenzyme A is also derived by successive beta oxidation of long chain fatty acids. Further metabolism of acetyl coenzyme A can occur in various ways:

(a) it enters Kreb's cycle,

(b) it is re-synthesized to long chain fatty acids,

(c) it is converted by liver (but not by other tissues) to ketone bodies (acetoacetate, beta hydroxy butyrate and acetone) which are utilized by peripheral tissues for energy production, and

(d) it is utilized for the synthesis of cholesterol and further derivatives of cholesterol such as bile salts, and adrenocortical and sex steroids.

In the post-prandial state, the liver converts the stored glycogen to glucose (Glycogenolysis) for release into circulation; it also converts non-carbohydrate sources (lactate, glucogenic amino acids and glycerol) to glucose (*Neoglucogenesis*). Neoglucogenesis occurs to a much smaller extent in the renal cortex. Diabetics show exaggerated neoglucogenesis especially from amino acids. The liver also converts other sugars such as fructose, galactose and sorbitol to glucose.

Thus, pyruvate metabolism (Kreb's cycle) is the meeting ground of the metabolism of carbohydrates, fats and proteins.

In health, out of the glucose derived from the daily ingested foodstuffs, about 3 per cent is stored in the liver and muscle as glycogen; about 30 per cent is converted to fatty acids; the rest enters Kreb's cycle and is utilized partly for energy production and partly for synthesis of amino acids.

INSULIN: Insulin is the hormone secreted by the beta cells of the islets of Langerhans and derives its name from the Latin word 'insula' which means an island. It was extracted from the pancreas by Banting and Best in 1921 and was isolated in crystalline form by Abel in 1930.

Chemistry: Insulin is a polypeptide with a molecular weight of about 6000, consisting of two amino acid chains, A and B, linked by two disulfide bridges. The chains contain 21 and 30 amino acids respectively, all in a known sequence. The 'active centre' of insulin has not been identified but the disulfide bridges are essential for its biological activity. Starting with porcine insulin, human insulin has now been synthesized in the laboratory. The present supplies of insulin are obtained from animal sources, mainly the pancreas of cattle. It is likely that in future, human insulin biosynthesized by cultures of bacteria (E. Coli) may be available for clinical use. Beef and pig insulin are structurally similar to human insulin in all except a few (3 and 1 respectively) amino acid residues. This explains their relatively low antigenicity when used in therapy. Between the two, pig insulin is even less antigenic than beef insulin in human beings.

Insulin is soluble in water but undergoes molecular aggregation at extremes of pH (3.2 and 10). Such aggregation is further encouraged by the presence of zinc which brings about crystallization of insulin. It is relatively insoluble at the pH range of 4 to 7. It can combine with protein such as protamine and with zinc with preservation of its biological activity and a prolongation of its duration of action. It adsorbs loosely to glassware and such adsorption can be inhibited by an excess of proteins especially albumen.

Synthesis and storage: The islets constitute 1 per cent by weight of the pancreas and there are some 2 million islets in the human pancreas; most of them are concentrated in the tail. They consist of alpha cells which secrete glucagon, beta cells which secrete insulin and D cells which secrete gastrin. Insulin is stored in the form of granules. Insulin content of pancreas parallels granulation of the beta cells. This storage is facilitated by zinc which makes insulin less soluble. The pancreas of a normal man contains about 4 units of insulin per gramme or a total of about 200 units (8 mg). A normal man probably secretes about 50 units of insulin daily, much of which is metabolized in the liver. It has been calculated that nearly 50% of the insulin released by the pancreas is removed during its first circulation through the liver. Hence, only about one half of what is produced reaches the peripheral circulation.

Insulin is synthesized within the betacells as a single chain polypeptide precursor called proinsulin, Proinsulin is biologically only 1/8th as active as insulin and forms only 3-6% of the total insulin within the pancreas. It is not stored within the beta cells but is soon cleaved by proteolytic enzymes after it has folded upon itself and the two disulfide bridges formed. Thus are formed the single chain C peptide and insulin made of A and B chains connected by two disulfide bridges (Fig. 59.2). Insulin is packaged within granules and stored in the beta cells from which it is continuously released at a slow rate into the circulation. The plasma level of insulin shows fluctuations throughout the day with peaks observed after meals.

Insulin release:

(1) *Glucose*: Glucose is the specific and most potent stimulus for insulin synthesis and release. A small rise in glucose concentration in the pancreatic artery leads to a release of pre-formed insulin and then to a stimulation of synthesis of more insulin by the beta cells. There appears to be threshold (50-90 mg%) for pancreatic arterial *plasma* glucose level (this corresponds to a *blood* glucose level of 45-80 mg%, as plasma glucose level is about 15% higher than blood glucose level) below which there is no glucose-induced stimulation of insulin release. As the plasma glucose level rises, there is a progressive stimulation of insulin release which reaches its maximum value with plasma glucose at 300-350 mg%. During intravenous glucose administration, the rise in plasma insulin level is very rapid and

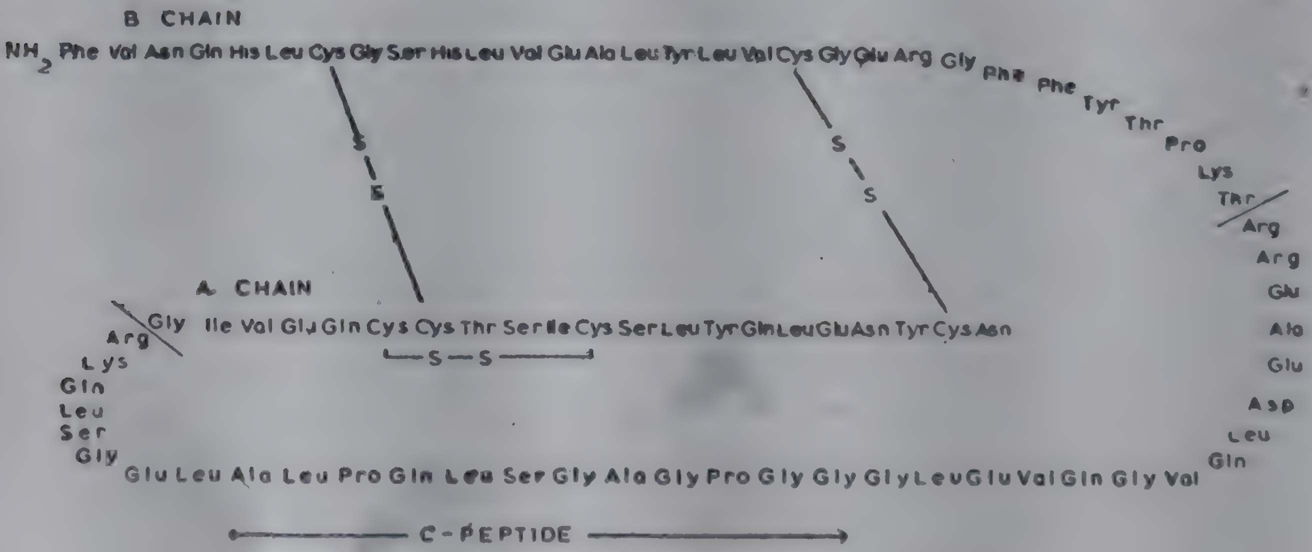

B CHAIN
NH2 Phe Val Asn Gln His Leu Cys Gly Ser His Leu Val Glu Ala Leu Tyr Leu Val Cys Gly Glu Arg Gly Phe Phe Tyr Thr Pro Lys Thr
S
S
S
S
A CHAIN
Gly Ile Val Glu Gln Cys Cys Thr Ser Ile Cys Ser Leu Tyr Gln Leu Glu Asn Tyr Cys Asn
S—S
Arg Arg Glu Ala Glu Asp Leu Gln
Arg Lys Gln Leu Ser Gly
Glu Leu Ala Leu Pro Gln Leu Ser Gly Ala Gly Pro Gly Gly Gly Leu Glu Val Gln Gly Val
C-PEPTIDE

Fig. 59.2: Human proinsulin, a precursor of insulin.

occurs within one minute. After ingestion of glucose, the rise is slower but to higher levels. The curve of plasma insulin after intravenous glucose administration is biphasic—a rapid, early rise followed by a steady and sustained one. It is believed that the ability of an animal to dispose of a glucose load is related mainly to the magnitude of the first peak of this biphasic insulin response.

Glucose is believed to act on a specific receptor, probably the adenyl cyclase system, on the cell wall of the beta cells. This then mediates the release of the stored insulin. This is independent of the action of glucose as a source of energy for the beta cells. The sensitivity of this insulin-releasing mechanism to glucose is dependent upon the prior carbohydrate intake by the animal. It is markedly depressd by restriction of dietary carbohydrate and by even short periods (48 hours) of fasting.

(2) *Other substrates*: Amino acids, especially arginine, stimulate insulin release probably by amplifying the action of glucose on the beta cells. In addition, fatty acids of all chain lengths, ketones and non-glucose sugars (fructose, mannose and ribose) also stimulate insulin release.

(3) *Gut hormones*: Gastrin, secretin, pancreozymin and enteroglucagon also stimulate insulin release. This might explain the much larger and more prolonged insulin response to oral than to intravenous glucose.

(4) *Other hormones*: Glucagon secreted by the adjacent alpha cells, stimulates insulin release. Growth hormone, thyroxine, ACTH, and glucocorticoids also stimulate insulin release. On the other hand, somatostatin, adrenaline, nor-adrenaline and exogenously administered insulin inhibit it.

(5) *C.N.S.*: The brain regulates insulin release probably by two pathways: (a) via the release of catecholamines and the hypothalamic releasing factors, and (b) via the autonomic nervous system. Insulin release is enhanced by parasympathetic (vagal) stimulation and by selective beta-adrenergic stimulation. It is inhibited by vagotomy and by alpha-adrenergic stimulation. This last factor probably acts by reducing the concentration of cyclic AMP in the beta cells; it is now accepted as the mechanism of inhibition of insulin release in conditions associated with an increased sympathoadrenal discharge viz. hypoxia, severe burns, surgery, myocardial infarction with shock etc. How much of the increase in the insulin secretion after food is mediated by the autonomic nervous system remains to be determined.

(6) *Drugs*: Glucose induced insulin release is enhanced by xanthines which inhibit phosphodiesterase, an enzyme which inactivates cyclic AMP. It is also enhanced by sulfonylureas. It is inhibited by the thiazides, diazoxide and diphenylhydantoin sodium.

Transport, fate and excretion: Insulin disappears rapidly from the plasma, its half life being about 5-6 minutes. The liver, kidneys, and the skeletal muscle take up most of the insulin. It circulates in the plasma partly protein bound and partly in a free, non-protein-bound form. In the presence of antibodies, however, insulin may be strongly bound to them. Insulin degradation is retarded in chronic renal disease and this may be important in determining insulin dosage in such patients.

Insulin is completely degraded by most of the tissues, especially by liver, kidneys, pancreas, testes and placenta. Only traces appear in the urine. The two chains are first separated by a reduction of the disulfide bridges by the action of glutathione-insulin transhydrogenase (insulinase) and are then further degraded by proteolytic enzymes.

Physiological and pharmacological actions: Actions of insulin are mostly studied by the administration of exogenous insulin to normal or insulin deficient animals or humans. It is easier to enumerate 'what' insulin does rather than to say 'how' it achieves this. There is no single action of insulin which accounts for the diverse effects it produces. Although carbohydrate metabolism is the one which is most extensively studied, insulin affects many aspects of energy metabolism in general. Many of its actions on protein and fat metabolism are independent of those on glucose metabolism.

Insulin needs the presence of intact cells for its biological effects which cannot be demonstrated upon subcellular fractions of any tissue. Insulin does not enter into the cell but acts on the cell membrane where it exerts two types of actions:

(1) It stimulates carrier-mediated transport of glucose, amino acids and potassium into the cell. This is not linked with the cyclic AMP system. The rise of intracellular glucose concentration to very high levels can by mass action stimulate many of the chemical reactions concerned in glucose utilization. In addition, insulin, by mechanism discussed below, directly stimulates certain aspects of glucose utilization within the cell. The increased uptake of amino acids and potassium by the cell is independent of the increased glucose uptake. The liver cells are freely permeable to glucose and apparently lack a carrier-mediated glucose-transport system; even then, insulin stimulates glucose uptake by the liver cells.

(2) Insulin binds to a specific receptor (which has been isolated from the liver and fat cells) on the cell membrane and causes the release of a 'second messenger' into the cell. The second mssenger alters the intracellular metabolic processes by altering the rates of synthesis of important enzyme proteins. This action is independent of the action on the carrier-mediated transport of various substances. One of the 'second messengers' is the cyclic AMP, the activity of which in liver and adipose cells is diminished by physiological concentrations of insulin. On the other hand, insulin leads to an increase in the synthesis of DNA, RNA and several key enzymes in intermediary metabolism in responsive cells.

The actions of insulin can be illustrated in three important susceptible target organs: liver, adipose tissue and skeletal muscle.

(a) **Liver:** In the liver, insulin increases the concentration of glucokinase (with resultant increased glucose uptake) and of glycogen synthetase (with resultant increased glycogen deposition) whereas it decreases the concentration of phosphorylase and cyclic AMP (with resultant decreased glycogenolysis) and of enzymes concerned with neoglucogenesis (with resultant decreased neoglucogenesis). Thus it promotes liver glycogen synthesis and storage. In its actions on the liver, insulin acts in concert with glucagon released by the pancreas. When the ratio insulin/glucagon release is high as after a meal, the net effect is increased glucose uptake and reduced glucose output by the liver. When the ratio is reversed, as in the post-prandial and fasting states and in severe diabetes, the glucose uptake by the liver is diminished and the glucose output is increased because of the reversal of the actions on the key enzymes in the liver. In contrast to insulin, glucagon enhances hepatic neoglucogenesis and glycogenolysis while diminishing glycogen synthesis.

Insulin also stimulates fatty acid synthesis and inhibits protein breakdown in the liver cells. In alloxan-induced diabetes in animals, it has been shown to stimulate mitosis and intense proliferation of the liver cells with a gain in the weight of the liver.

(b) **Adipose tissue:** Ordinarily, the fat cell membrane can exclude glucose; insulin changes its permeability and promotes uptake and utilization of glucose. The latter leads to increased synthesis of glycerol, alpha-glycerophosphate and fatty acids. The last two combine to form triglycerides (Lipogenesis). Triglycerides represent a storage form of fat within the adipose cell. Glycerophosphate binds free fatty acids the release of which from the adipose tissue is therefore reduced (Antilipolytic action). Insulin exerts its antilipolytic action also by inhibiting the cyclic AMP system in the adipose tissue. Antilipolysis occurs faster and requires lower concentrations of insulin than lipogenesis. Insulin stimulates lipoprotein-lipase on the surface of the adipose tissue cells. The latter hydrolyses the chylomicrons in circulation. The released free fatty acids enter into the cells and combine with glycerophosphate to form triglycerides. The glycerol and protein components are rejected into circulation.

(c) **Skeletal muscle:** Insulin stimulates glucose transport into muscle cells. The intracellular glucose is then utilized by the glycolytic pathway and partly by glycogen synthesis. It stimulates the transfer of amino acids into the cell and their incorporation into proteins (protein anabolic action). In addition, it inhibits proteolysis and lipolysis in the muscle.

The biological effects of insulin are thus predominantly concerned with the carbohydrate, fat and protein metabolism of the tissues.

Effects on carbohydrate metabolism and regulation of blood glucose level: The Folin and Wu method of blood 'sugar' determination, commonly used in clinical practice, estimates certain non-glucose substances in addition to glucose. The blood 'sugar' value is therefore higher than the blood 'glucose' value by 20-30 mg%. The blood 'glucose' values are obtained by the specific glucose oxidase method. The 'true sugar' values obtained by the Nelson-Somogyi and the auto-analyzer methods, closely approximate the blood 'glucose' values. The arterial blood glucose concentration is higher than the venous glucose concentration in the fasting as well as the fed state.

In health, the fasting venous blood glucose fluctuates between 60 and 100 mg per cent. After food, it rises to a maximum of 140-150 mg per cent and returns to the fasting level within 2-3 hours. In health, the blood glucose shows hardly any change during prolonged intravenous infusions of glucose at the rate of 125 mg/minute (0.1 g/kg/hour in a 70 kg man). The arterial blood glucose is maintained so as to exceed the 'tissue threshold level' and to supply glucose to brain which can utilize only glucose as its fuel. Some other organs (renal medulla, R.B.Cs. and bone marrow) also utilize glucose alone but their total glucose needs (40 g/day) are relatively smaller than that of the brain (120 g/day) alone.

The maintenance of blood glucose is achieved by a large number of simultaneously occurring physiological processes, their relative rates varying at different times. The main determinants of the variations in their relative rates are ingestion of food and the plasma levels of various hormones especially insulin. The central theme of all these processes is (a) to promote storage of glucose as well as its peripheral utilization after a carbohydrate meal, and, (b) to make glucose available to the brain by glycogenolysis and neoglucogenesis, and free fatty acids to the other tissues, in the post-prandial state. Thus,

(1) Ingestion of a mixed meal results in the release of gut hormones (gastrin, pancreozymin, secretin and enteroglucagon) into portal circulation. All these induce insulin release in addition to influencing their specific target tissues. Of them, only pancreozymin enhances glucagon release.

Absorption of food results in elevation of blood glucose, amino acids and free fatty acids. All of them induce insulin release. Glucagon release is enhanced by amino acids but is inhibited by hyperglycemia and free fatty acids.

It must be remembered that both insulin and glucagon are released into portal circulation and, therefore, reach the liver in high concentrations. The overall effect of food ingestion and absorption is to tilt the release of insulin and glucagon in favour of insulin. The reverse occurs during the post-prandial period, during starvation and in severe diabetes.

Thyroxine helps at this level by promoting the gastrointestinal absorption of glucose.

(2) The liver plays a central role in regulation of the blood glucose level. The enhanced insulin/glucagon release ratio during absorption of food stimulates glucose uptake and inhibits glucose output by

the liver by mechanisms already discussed. This helps to curb the rising blood glucose level.

The reversal of insulin/glucagon release ratio in favour of glucagon in the post-prandial state increases the hepatic glucose output. In the fasting state, this is aided further by extra-pancreatic anti-insulin hormones. Gluconeogenesis is stimulated by GH, corticosteroids and catecholamines whereas glycogenolysis is stimulated by catecholamines. The thyroid hormones encourage neoglucogenesis.

(3) The insulin induced stimulation of utilization of glucose by the muscles and the adipose tissue tends to lower the blood glucose. During the hours of plenty, glucose is the main fuel for energy as well as storage in the tissues.

The peripheral utilization of glucose results in the production of CO_2, water, heat and important substances such as pyruvate, TPNH, DPNH and ATP. Many of the biochemical defects of insulin deficiency can be explained on the basis of deficiency of these substances. Insulin is not necessary for glucose uptake by brain, leucocytes and R.B.Cs, for its gastrointestinal absorption nor for its renal tubular re-absorption. The most easily demonstrable effect of insulin deficiency is hyperglycemia although its other effects (on fat and protein metabolism) are equally important.

In the post-prandial state, all the anti-insulin hormones (glucagon, GH and catecholamines, with glucocorticoids playing a permissive role) stimulate lipolysis with release of free fatty acids into circulation. The tissues (except the brain, RBCs, renal medulla and bone marrow) switch over to fatty acids as the main metabolic fuel and thus conserve glucose. Conservation of glucose is further aided by the inhibitory action of catecholamines and free fatty acids on tissue uptake of glucose; whereas the protein anti-anabolic action of glucocorticoids makes amino acids available for neoglucogenesis by the liver. This hormonal-metabolic profile of the post-prandial state is further exaggerated during prolonged fasting as well as in severe insulin deficiency as occurs in severe uncontrolled diabetes.

(4) During pregnancy, the dominant theme is to make plenty of food (glucose) available to the fetus. The energy metabolism of pregnancy is, therefore, characterized by an excess of anti-insulin influences from mother's own adrenal cortex as well as from the placenta. During pregnancy, the fasting blood glucose is a little lower and blood glucose during absorption of a meal a little higher than during the non-pregnant state. Pregnancy is thus a potentially diabetogenic condition.

(5) Removal of glucose by the lactating breast for milk production and the wasteful urinary loss in the rare syndrome of renal glycosuria are the other factors affecting blood glucose level.

Effects on lipid metabolism: As discussed earlier the net effect of insulin antilipolytic, fat synthesizing and glycerogenic actions is to enhance total fat storage. The weight gain occurring on insulin administration, in contrast to that on HGH administration, has increased adiposity as its important component. One of the earliest defects in diabetes (seen even before the abnormality of carbohydrate tolerance) is abnormal plasma FFA (free fatty acid) levels in the overnight fasting state and after exercise. In the decompensated diabetic state, the greater availability of FFA (from enhanced lipolysis in adipose tissue and muscle) leads to the synthesis of more ketone bodies by the liver than can be utilized by the peripheral tissues. The FFA and the ketone bodies (mainly acetoacetic acid) are responsible for the ketoacidosis and possibly for the insulin resistence seen in this condition.

Effects on protein metabolism: As discussed above, insulin is an important protein anabolic hormone. Its deficiency leads to negative nitrogen balance by reducing the peripheral protein synthesis and by diverting the amino acids for neoglucogenesis. This is a wasteful method of producing glocose as only 56 g of glucose can be produced from each 100 g of protein broken down. In addition, insulin is necessary for the anabolic action of GH to become effective.

Since insulin influences such a wide range of metabolic actions, it is not surprising that insulin deficiency has damaging effects on practically every organ and tissue in the body.

Plasma insulin: Plasma insulin can be measured by radioimmune assay (IRI or immunoreactive insulin) and by bioassay (ILA or insulin like activity). The latter utilizes either rat diaphragm or adipose tissue for assay and the insulin activity of the unknown sample is judged by one of the several ways, such as utilization of glucose, increase in glycogen deposition, liberation of radioactive carbon dioxide or inhibition of lipolysis. For several reasons, results obtained by different methods do not agree with each other.

IRI: This would, at present, appear to be the closest approximation to plasma total insulin. It measures both insulin and proinsulin in healthy individuals; the fasting level of IRI is 5-30 μu-per ml of plasma (mean of 20 micro. u. per ml). It rises sharply on intravenous glucose administration and less sharply but to higher levels on ingestion of glucose. Following the administration of glucose to those with mild, maturity onset diabetes, the rise of plasma IRI is sluggish for the first half an hour but it reaches hypernormal levels after one hour (*hyperinsulin response*).

Some workers believe this sluggish, initial response of plasma IRI to be the primary defect in genetic diabetes and the subsequent hyperinsulin response to be due to the excessive rise of plasma glucose permitted by the inadequate initial rise of IRI. Other workers look upon the hyperinsulin response as a compensation for peripheral insulin insensitivity. A hyperinsulin response is also seen in some non-diabetic obese individuals.

A *hypoinsulin response* is, on the other hand, seen in patients with juvenile onset diabetes, those with diabetes due to pancreatectomy or chronic pancreatic disease, and those with severe maturity-onset diabetes whether untreated or treated for a long time.

Proinsulin constitutes 1-2% of the total plasma insulin immediately after a glucose load but 5-28% 2 hours later. It is also high in other situations where the rate of insulin synthesis and release is high: stimulation by arginine or tolbutamide, obesity, diabetes due to acromegaly. It is unlikely that it represents a defect in

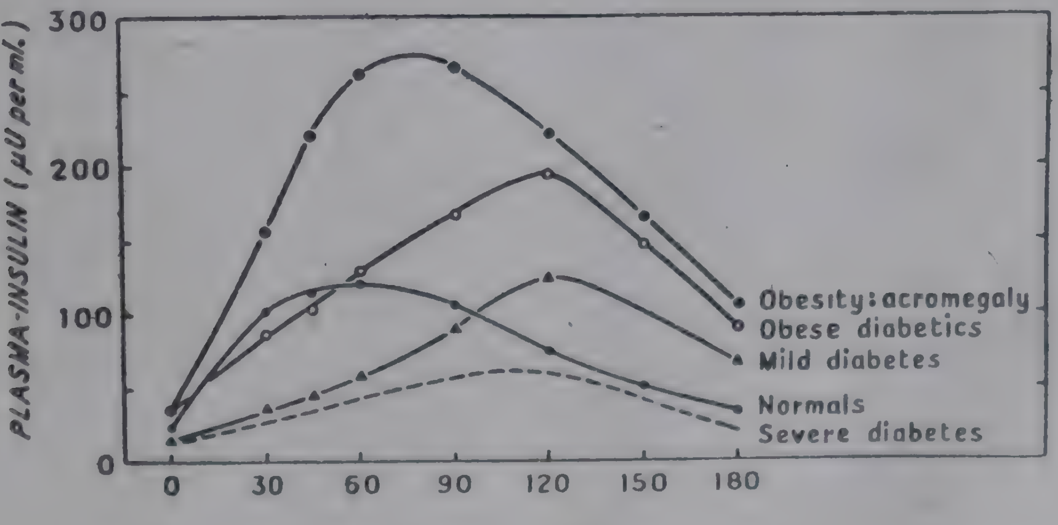


Fig. 59.3: Plasma insulin responses to oral glucose (100 g.). Reproduced from "Catt, K. J. An ABC of Endocrinology". Publ. the Lancet Ltd. London.

hydrolysis of proinsulin to insulin. Very high plasma levels of proinsulin are seen in patients with insulinoma.

ILA: The term 'Insulin-like activity' is used to indicate what is measured by the bioassay procedures because the effect is the sum total of insulin itself, its potentiators and inhibitors. The adipose tissue methods give higher ILA values than the diaphragm method. ILA, as measured by rat diaphragm method, is only partially suppressed by insulin antibodies. The amount of suppressible ILA corresponds to the IRI.

Factors modifying the actions of insulin:

(a) *Muscular exercise*: Muscular exercise causes lowering of blood glucose by enhancing entry of glucose into the muscle cells. It has been claimed that this is due to release of bound insulin from the muscle or its vasculature.

(b) *Other hormones*: as discussed earlier.

(c) *Insulin antibodies*: Specific anti-insulin antibodies are present in the plasma of all individuals who have received insulin injections. In a few individuals, however, their presence is accompanied by 'insulin resistance' requiring more than 200 units of insulin per day.

(d) *Synalbumen fraction of Vallance-Owen*: An albumen-associated insulin antagonist has been demonstrated in low concentrations in the serum of non-diabetics and in higher concentration in the serum of diabetics, pre-diabetics and individuals with myocardial infarction. It probably consists of the beta chain of insulin bound to albumen and is believed to block the insulin action on transport of glucose into cells. Some workers believe it to be the genetic marker of diabetes. It is not detected in the plasma of hypophysectomised diabetics. In passing, it must be mentioned that some authorities have recently doubted the existence of this synalbumen factor.

Absorption, fate and excretion: Insulin, given orally, is ineffective as it is destroyed by gastrointestinal enzymes. It must be given parenterally.

Addition of zinc, of protein, or of zinc and protein slows down its absorption and prolongs its duration of action. Labelled insulin when injected is taken up mainly by the liver and kidney.

Preparations and dosage: The details of various insulin preparations are shown in Table No. 59.1. Plain insulin is commonly

Table 59.1: **Insulins in Common Use**

Preparation	pH and appearance	Protein	Activity in hours		
			Onset	Peak	Duration
	SHORT ACTING				
Plain I.P.	3.2, clear	—	1	4	8
Insulin zinc suspension, amorphous* (semi lente)	7.2, cloudy	—	1	8	14
	INTERMEDIATE ACTING				
Isophane (NPH) B.P.	7.2, cloudy	Protamine	2	12	24
Insulin zinc suspension,** I.P. (lente)	7.2, cloudy	—	2	6-8	24
Globin, I.P.	3.4, clear	Globin	4	6-10	18
	LONG ACTING				
P.Z.I., *** I.P.	7.2, cloudy	Protamine	7	16	36
Insulin zinc suspension, crystalline* (ultra lente)	7.2, cloudy	—	7	16	36

*Mixed only with insulin zinc suspensions.

**A mixture of 3 volumes of insulin zinc suspension, amorphous and 7 volumes of insulin zinc suspension, crystalline.

***Mixed only with crystalline insulin.

injected about ½ hour before each major meal. The intermediate and long acting preparations are injected once a day before the breakfast.

Insulin mixtures: The action of short acting insulins is so short that several injections per day are required to control diabetes adequately. The action of long acting insulin starts too late to cover the first meal of the day (breakfast) when an injection is taken in the morning. Hence, appropriate mixtures of the two are commonly used in practice. Such mixtures have a fairly rapid onset and act for about 24 hours. They are given before breakfast. The commonly used mixtures are:

(1) PZI and plain insulin (1 part: 2 to 3 parts). PZI contains a certain amount of free protamine which combines with added plain insulin. Hence, at least 2 parts of plain insulin must be added to 1 part of PZI as otherwise, the mixture behaves like PZI only.

(2) NPH insulin (which is a modified protamine zinc insulin) contains just enough protamine to combine with insulin. It behaves like a 1:3 mixture of PZI and plain insulin. If necessary, plain insulin or Nuso can be mixed with it before injection.

(3) Lente insulin: A readymade mixture of amorphous (semi lente) and crystalline (ultra lente) insulin zinc suspensions in the proportion 3 to 7.

Insulin mixtures except lente are unstable and must be prepared just before use. The procedure, however, is too complicated for some patients to follow. Their main advantage is that they can be tailor-made to suit the requirements of an individual patient. Because the properties of lente insulins depend upon the neutral pH 7.2, plain insulin with a pH 3.2 should not generally be mixed with lente insulin except immediately before injection and even then the plain/lente ratio should be less than 1:1 (preferably 1:2 or less). Nuso or Actrapid can be freely mixed with lente insulin.

Newer Insulins: These insulin preparations have the following characteristics:

(1) They are purer than the older preparations; proinsulin and the intermediate breakdown products of proinsulin have been removed. The purity is highest in monocomponent insulins.

(2) They are all neutral and less likely to cause subcutaneous fat atrophy. It is possible to mix neutral, regular insulin with any of the modified insulins in any proportion.

(3) They are more stable and do not require refrigeration.

(4) Some of them are of porcine origin alone and therefore, are less antigenic. They can be used effectively in patients allergic to beef insulin and in those with circulating antibodies to beef insulin. In the last case, when changing from an older insulin preparation to a newer, porcine insulin, the dose should be reduced in order to avoid hypoglycemic episodes.

(5) All are expensive at present, and not freely available. The preparations are:

(a) *Nuso*: This is bovine insulin in a clear, neutral solution.

(b) *Rapitard* ('Biphasic Insulin B.P.'): This is a cloudy mixture of actrapid (1 part) and large, insoluble crystals of bovine insulin (3 parts), buffered to pH 7.0. It is pro-insulin freed insulin. Its action is similar to that of lente insulin but the onset of action is quicker and the control of blood sugar is said to be smoother than with the latter.

(c) *Actrapid*: This is a clear neutral solution (pH 7.0) of recrystallized monocomponent porcine insulin. Because of its neutral pH, it acts faster than plain insulin and is less irritating to the tissues than the 'acid' insulins.

(d) *Monotard*: This monocomponent insulin zinc suspension contains highly purified porcine insulin claimed to be devoid of any antigenic property in humans even during prolonged use.

Adverse reactions:

(a) **Hypoglycemia:** Hypoglycemia is a common adverse effect of insulin and is an extension of its pharmacological action. The common causes of hypoglycemia during insulin therapy are: too large a dose of insulin, failure to eat, violent unaccustomed physical exercise and ingestion of alcohol. It is especially frequent in juvenile and in aged diabetics and in diabetics with renal failure.

With short acting insulins, hypoglycemia occurs about 3 hours after its administration. With intermediate acting insulins, it tends to occur in the mid or late afternoon. With long acting insulins, it occurs in the early hours of morning.

Symptoms of hypoglycemia are of two types: (1) *Cerebral*, due to the brain being starved of glucose; they consist of confusion, bizarre behaviour, depression, coma, convulsions and focal lesions such as hemiplegia or visual disturbances. Cerebral edema or organic damage may cause these symptoms to persist after correction of the low blood sugar level; and (2) *Sympathetic*, due to epinephrine liberation; these are vasoconstriction, tachycardia, palpitation, tremulousness, pallor, sweating, piloerection and subjective feeling of impending disaster. The body temperature tends to be lowered in hypoglycemic coma and this is of diagnostic importance.

With rapid acting insulins, the sympathetic symptoms predominate. With intermediate acting insulin, they are minimized whereas the cerebral symptoms predominate; moreover, they are gradual in onset and may not be recognized as due to hypoglycemia. With long acting insulin, the hypoglycemic symptoms occur during sleep and consist of nightmares, sweating and a headache on waking up.

Attacks of hypoglycemia must be prevented because (a) they are harmful in patients with cardiovascular disease, (b) frequent attacks may cause permanent neurological damage, and (c) an unrecognized attack during night is followed by rebound hyperglycemia with glycosuria next morning (Somogyi effect); this is likely to lead to an increase in the dose of insulin with a worsening of the condition.

Patients on insulin therapy should be carefully explained the symptoms of hypoglycemia. They should be warned about the dangers of missed meals, violent exercise and alcohol. They should carry some sugar with them at all times and swallow it at the first symptom of hypoglycemia. Finally, a patient on insulin should be forbidden to swim, to work near machines and to drive till the dose is stabilized.

Oral glucose can relieve hypoglycemic symptoms if it is administered early. In a comatose patient, intravenous glucose or intramuscular glucagon (1 mg) rapidly awaken the patient. If coma persists after correction of hypoglycemia, mannitol should be administered intravenously to relieve the cerebral edema.

A coma in a diabetic that is not diagnosable with certainty should be first treated with intravenous glucose (50 ml of 50 per cent). A rapid arousal while the injection is being given confirms the diagnosis of hypoglycemia.

(b) **Insulin allergy:** Allergy to insulin is infrequent. It may consist of local itching, redness, swelling and pain at the site of the injection. Generalized urticaria and lymphadenopathy are less common. Anaphylactic reactions are very rare. Allergic reactions may be due to insulin itself or to protamin in the preparation. Hence non-protein containing insulins such as lente insulin are preferred. Pork insulin which is antigenically different is used in place of the commonly used beef insulin in such patients.

(c) **Insulin lipodystrophy:** It consists of atrophy of subcutaneous fat at the sites of frequent insulin injections, resulting in irregular depression in the skin and subcutaneous tissue. Further absorption of insulin from such sites is erratic and a changeover to a new site may produce hypoglycemia with the same dose. Lipodystrophy is best prevented by frequently changing the site of injections.

(d) **Insulin presbyopia:** When a diabetic is rapidly controlled with insulin, he often develops loss of visual accommodation due to alterations in the physical properties of the lens. It usually settles down within a few weeks and new glasses should not be prescribed until a stable refractive error is achieved.

(e) **Insulin neuropathy:** In an occasional patient, rapid control of diabetes with insulin either precipitates peripheral neuropathy or worsens a pre-existing one. The mechanism of this phenomenon is not known.

(f) **Obesity:** Insulin therapy, if used alone and without dietary restriction, may increase the body weight in the already obese diabetic patients. This increases the insulin requirement and sets up a vicious cycle.

Therapeutic uses of insulin:

(1) In idiopathic diabetes mellitus: discussed below in detail.

(2) Secondary diabetes: Diabetes due to pancreatic diseases such as pancreatitis or hemochromatosis generally needs to be treated with insulin. Diabetes associated with acromegaly or Cushing's syndrome generally responds to oral antidiabetic drugs and to the treatment of the primary disease.

(3) In schizophrenia: Insulin coma is induced in schizophrenia as a therapeutic measure. The coma is allowed to last for 20-30 minutes and then terminated by giving glucose by stomach tube or I.V. Usually 30-50 comas are produced. It is important that patients should be observed for convulsions during such therapy.

(4) In the past it was used for improving appetite and increasing body weight. Its use for this purpose is no longer recommended.

(4) Insulin tolerance test with determination of plasma HGH is used to test pituitary reserve and to diagnose hypopituitarism.

PHARMACOTHERAPY OF DIABETES MELLITUS

With the introduction of insulin, oral antidiabetic drugs and antibiotics, diabetes is no longer a dreadful disease and with proper management with diet, drugs and exercise a diabetic can enjoy almost a normal life. The etiology of this condition, however, is still obscure although it definitely has a hereditary tendency.

The experimental pancreatic diabetes, produced in dogs by total pancreatectomy, differs from the clinical diabetes in its low insulin requirement. It is ameliorated by hypophysectomy and/or adrenalectomy. Selective destruction of beta cells of the islets of pancreas of rats and rabbits by agents like alloxan, uric acid, or dehydroascorbic acid produces relatively more severe diabetes. Pathogenesis of diabetes mellitus in humans, however, is different from that in these experimental conditions.

In the early stages, the maturity onset diabetics, especially the obese ones, have an excess of insulin in their plasma in response to a glucose load (Fig. 59.3). This is probably the consequence of a peripheral insulin resistance on the part of the obese adipose cells; the insulin sensitivity becomes normal after weight reduction in these obese patients. The resistance is believed to be due to defective binding of insulin to the obese adipose cells.

On the contrary, the plasma of the juvenile diabetics lack demonstrable insulin. The juvenile diabetics behave like pancreatectomized animals. Recent evidence suggests that the destruction of the pancreatic islets may be due to 'insulitis', an autoimmune lesion probably initiated by certain virus infections. Islet cell antibodies have been demonstrated in the plasma of some of these patients. Certain HLA phenotypes have been found to be present commonly in the juvenile diabetic patients.

Some evidence suggests that the alpha cells of the islets of Langerhans also show abnormal function in diabetic patients. Thus in diabetics (a) plasma levels of glucagon are high especially in ketoacidosis, (b) the response to amino acids is excessive and (c) the suppression of plasma glucagon level by hyperglycemia is inadequate. Whether these abnormalities of glucagon secretion are of any importance in the pathogenesis of diabetes is not certain.

Clinically, there are various types of diabetes mellitus. One of these occurs in obese, elderly persons, where it starts in adult life, is stable and less likely to cause ketoacidosis. The juvenile type, on the other hand, occurs in younger, underweight persons, in whom it often starts during the period of body growth, is labile and is often complicated by ketoacidosis. Insulin can be extracted from the pancreas of maturity onset diabetics but none from those with juvenile type of patients. Thus, in juvenile type of diabetes, there is an absolute deficiency of insulin and hence, it tends to be more severe. Other varieties usually lie in between these two extremes.

In the absence of insulin, there is a marked reduction in the transfer of glucose into certain cells; glycogen synthesis from glucose diminishes; protein is converted to glucose at abnormally high rates and the nitrogen residue is excreted in the urine as large amounts of urea; hyperlipidemia and ketosis occur. If there is accompanying infection, the plasma levels of anti-insulin hormones (catecholamines, cortisol and glucagon) rise to high levels. Administration of insulin corrects all these metabolic and hormonal abnormalities.

Pancreatic diabetes, if left untreated, can lead to the impairment of general health, increased susceptibility to infections, retinal, renal, cardiovascular and neurological complications and diabetic coma. Hence, early detection and prompt treatment are absolutely essential to achieve good therapeutic results. The aims of therapy are:

(a) To control symptoms adequately with diet, exercise and drugs.

(b) To maintain the optimum body weight.

(c) To correct the metabolic disturbances and

(d) To prevent or delay the degenerative vascular complications.

An ideally controlled diabetic individual:

(1) Should be free from classical diabetic symptoms of polyuria, polyphagia and polydipsia.

(2) Should have almost normal expected weight for his/her age.

(3) Should have blood glucose levels as near normal (fasting 110 mg% and post-prandial 130 mg%) as is possible without getting hypoglycemic episodes. *This means that in old people and in patients with severe liver and kidney disease, cardiac disease and cerebrovascular disease, one often has to be satisfied with higher levels of blood glucose.* In such patients, if the renal threshold is not elevated, one may aim at a minimum glycosuria (say less than 5-10 g/day). A similar compromise is generally necessary in the juvenile diabetes in order to avoid hypoglycemic episodes.

(4) Should never develop ketonuria and

(5) Should maintain optimum linear growth during childhood.

Education of the patient is very important in the successful management of the disease and must include an understanding of: his own disease, urine examination, insulin administration, adjustment of the insulin dosage, the danger of neglecting the disease and the rewards of conscientious adherence to the prescribed regimen.

The diet should be adjusted to bring the weight of a diabetic (up or down) to his optimum weight and to maintain it there. Obese diabetics must be encouraged to lose weight as this is accompanied by considerable improvement in carbohydrate tolerance. In growing children, it must take into account their continually changing caloric requirements. Usually it includes 0.5 to 1 g. of protein per kg. body weight per day and about 150-200 g. of carbohydrates, the rest of the calories being made up from fat. Sugar and sugar containing foods must be avoided. The total daily intake should be divided into three rather than two meals and the distribution of carbohydrates and calories among the three meals should be constant from day to day. Over-eating and fasting must be avoided.

Daily, regular, physical exercise reduces insulin requirements. Sudden, unaccustomed violent exercise, however, is likely to precipitate hypoglycemia and should be avoided and if it is unavoidable, extra food should be taken prophylactically.

Not all diabetics need insulin. Some can be controlled on diet alone. The indications for insulin therapy are:

(1) Juvenile diabetes, certainly all those with disease of more than 2 years duration.

(2) Maturity onset diabetics who are underweight, those who have a history of onset below 30-35 years and those in whom diabetes is of very long standing.

(3) All diabetics with complications such as ketosis, infection, intractable pruritus, gangrene, congestive cardiac failure or progressive retinopathy.

(4) During surgical procedures.

(5) Diabetic coma and pre-coma.

(6) Primary or secondary failure following sulfonylurea therapy, and

(7) In the past, pregnant diabetics were always treated with insulin. It is now thought permissible to treat the mildest cases with oral drugs and all others with insulin.

Choice of insulin preparation: For routine control of maturity onset diabetes, one of the intermediate acting preparations is most commonly used. It can control most diabetics with a single daily injection, commonly given before breakfast. An appropriate insulin from the short or long acting group may be added if this does not give the desired degree of control. Lente insulin is preferred to PZI and NPH because of the possibility of allergic reactions due to protamine in the case of latter two products. On the other hand, NPH insulin is preferable to lente insulin when it is necessary to add plain insulin to it for better control.

The main merits of plain insulin are its rapidity of action and short duration. This makes it convenient when a rapid action is required as in diabetic coma and when it is desirable to regulate the dose frequently as in juvenile and unstable diabetes and post-operatively. For the same reason, it must be used when an illness such as an infection, vomiting or diarrhoea prevents regular intake of meals and the patient is likely to get hypoglycemia with longer acting insulins. It must also be used when the total daily requirements of insulin exceed 60-80 units as the use of an intermediate acting preparation is likely to give rise to severe hypoglycemic reactions. When it is decided to change over from short to intermediate acting insulin in a patient, it is desirable to commence therapy with a dose of the latter only 2/3rds of the total daily dose of the former.

Insulin therapy: Every diabetic may require insulin at some time in his life and it is life-saving in some situations. Although no insulin preparation available can mimic the need-oriented supply of insulin by the patient's own pancreas, majority of diabetics can be managed by an intelligent use of the available preparations.

(a) **Management of an adult with maturity-onset type of diabetes without any complication:** In most such patients, diabetes is stable and relatively mild. They can be controlled with diet alone or with diet and oral antidiabetic drug. If insulin is preferred for any reason, an intermediate acting insulin (lente, NPH) is the preparation of choice. Treatment may be initiated with 10-20 units given subcutaneously half an hour before breakfast. Urine is examined for glycosuria as follows: fasting, before lunch, before dinner and at bedtime. The dose of insulin is increased by 4 units once every 3-4 days as long as glycosuria persists in the predinner urine samples or till 60-80 units are reached. If glycosuria then persists in the pre-lunch urine, a small dose of a short acting insulin (plain or semi-lente, as the case may be) is added to the morning dose. Persistence of glycosuria in the bedtime sample is treated by giving an additional dose (8-12 units) of plain insulin before dinner. Also, if lente insulin before breakfast does not control next morning's fasting glycosuria while abolishing the daytime glycosuria, the dose should not be increased any further as otherwise, day time hypoglycemia is likely to occur. Instead, a small additional dose of lente or NPH insulin may be given before dinner. A few patients may ultimately need a mixture of plain and NPH (or lente) before breakfast and before dinner for a round the day control of glycosuria and hyperglycemia. In some of these patients addition of a biguanide may help to improve the diabetic control.

(b) **Management of an adult, maturity-onset diabetic with complications such as acute infective illnesses:** Under these conditions, insulin requirements go up and if the disease is not adequately treated, ketoacidosis is likely to develop. If the patient can continue to take his normal food, the insulin regimen need not be changed. If the patient cannot take his normal food, he must be given a liquid diet containing plenty of salt and about 200 g. of carbohydrates per day. He is encouraged to take portions of this every 3-4 hours and plain insulin (10-50 units) is given subcutaneously every 6 hours after appropriate urine examinations. Salted buttermilk, meat soup, milk, fruit juice, and added quantities of glucose are suitable items of food for these patients. As soon as the patient can take solid food, he is returned to his original insulin regime.

(c) **Juvenile diabetes:** Juvenile diabetes tends to be unstable and attacks of diabetic coma and hypoglycemia are liable to occur frequently in this condition because these patients tend to be unpredictable in their eating habits, sporadic in their exercise and prone to emotional outbursts, all of which interfere with the smooth control; added to this are the over-anxious and over-solicitous parents of a diabetic child.

If properly instructed and adequately motivated, some juvenile diabetics can co-operate sufficiently to be controlled by a single daily pre-breakfast injection of NPH or lente insulin; this is, however, an exception rather than a rule. Many patients need either (a) an injection of plain insulin before each major meal or (b) a mixture of plain with NPH (or lente) insulin before breakfast and dinner.

Isophane

Insulin resistance: Insulin resistance is defined as the daily requirement of insulin in excess of 200 units. Such resistance may be due to (a) insulin antibodies. Insulin antibodies develop in all persons who receive the available preparations of insulin except perhaps monocomponent insulin. *They are likely to develop in high titres in patients who have received insulin intermittently rather than continuously* (b) associated endocrine disorders such as acromegaly, adrenal hypercorticism or pheochromocytoma or (c) lipoatrophic type of diabetes. The two latter conditions are rare causes of insulin resistance.

Insulin resistance due to antibodies responds to glucocorticoids. Prednisolone in the dose of 60-100 mg. daily is usually employed. Some cases of resistance however, are 'idiopathic'. In such cases, insulin is continued in as large doses as aro required in the hope that insulin sensitivity may return spontaneously as it some times does for no apparent reason. In some of these patients, addition of a sulfonylurea or a changeover from beef to pork insulin may hasten such return of insulin sensitivity.

MANAGEMENT OF METABOLIC COMA IN THE DIABETIC

(A) Keto-acidotic diabetic coma:

In ketosis prone juvenile diabetes, diabetic coma can be precipitated by merely omitting insulin. In maturity onset diabetes, it is generally precipitated by a severe infection which causes the plasma levels of anti-insulin hormones (catecholamines, cortisol and glucagon) to rise.

Pathophysiology: The deficiency of effective insulin action under these circumstances brings about (a) failure of glucose entry into peripheral tissue cells, leading to hyperglycemia; this is abetted by neoglucogenesis, (b) excessive mobilization of fatty acids from the adipose tissue, leading to excessive production of ketone bodies: acetoacetic and beta-hydroxy butyric acids. These acids contribute to metabolic acidosis and by being excreted as salts of sodium and potassium in the urine, deplete the body sodium, potassium and water;

(c) impaired oxidation of glucose leading to the non-availability of pyruvate. Acetate is used preferentially for conversion to aceto-acetate, thus aggravating ketoacidosis;

(d) increased mobilization of muscle protein, increased hepatic neoglucogenesis and increased urinary excretion of nitrogen;

(e) increased hepatic glycogenolysis resulting into depletion of liver glycogen.

Hyperglycemia and glycosuria promote a solute diuresis and this leads to dehydration and hypovolemia which aggravate the acidosis further.

The urine is loaded with sugar and ketone bodies and even the breath smells of acetone. The blood sugar is commonly in the region of 600-800 mg. per cent. The plasma ketones are sufficiently elevated to give a markedly positive reaction of undiluted plasma with acetone test powder (Duncan's test). The CO_2 combining power is markedly reduced and the blood pH is lowered.

Management: The diagnosis must be confirmed before treatment is commenced. If hypoglycemic coma cannot be ruled out, the effect of intravenous glucose (50 ml of 50 per cent) should be tried first.

On admission, blood is withdrawn for the following estimations, which must be repeated every 2 hours: glucose, CO_2 combining capacity, serum potassium and hematocrit.

The following clinical data are recorded on admission and one hourly after that: pulse rate, blood pressure, temperature, fluid intake and output, glycosuria, ketonuria and ketonemia (by Duncan's test).

The general principles of management are:

(1) early and proper use of insulin,
(2) rapid fluid replacement,
(3) correction of severe acidosis,
(4) treatment of infection, if any,
(5) prevention of hypokalemia by timely administration of potassium during recovery and
(6) excellent nursing care.

(1) *Insulin*: In the past, large doses of insulin (50-100 units) were administered every 2-4 hours, initially intravenously and then subcutaneously, in the belief that ketoacidosis caused insulin resistance. Recent work has failed to demonstrate the existence of such pH dependent insulin resistance. In most instances the 'resistance' can be accounted for by the following factors; (a) failure of absorption of subcutaneous insulin due to dehydration and circulatory failure; (b) the presence of infection with an excess of anti-insulin hormones; (c) the time taken by insulin to change the pattern of hepatic enzymes from one of insulin deficiency (neoglucogenesis stimulated) to one of insulin plenty (neoglucogenesis inhibited and glycogenesis stimulated). Thus, patients with infection respond more slowly than those without infection.

It is now known that the maximal biological effects of insulin are achieved by a plasma concentration of 100-200 microunits/ml. In diabetic coma, the maximum clinical benefit would accrue from the continuous maintenance of these maximum physiological levels of plasma insulin. Because of the short plasma half life (5-6 minutes) of i.v. insulin, this can be most effectively achieved by a continuous, intravenous infusion of regular insulin at the rate of about 0.1 unit/kg/hour (*Low Dose Insulin Therapy*).

Large subcutaneous doses often fail to be absorbed and large (50-100 units) intravenous doses give widely fluctuating plasma levels of insulin: 1000 μu/ml immediately after injection and less than 30 μu/ml, after half an hour. This means that with such i.v. doses, decline in blood glucose is very rapid initially but may cease completely after 1/2 hour. Further, the rapid initial decline in blood glucose can cause a rise of anti-insulin hormones. The rapid decline in blood glucose pushes a lot of potassium into the muscle and can cause hypokalemia. Finally, a rapid correction of acidosis (abetted by administration of large doses of alkali) can cause cerebral edema.

Thus, in contrast to high dose insulin therapy, low dose insulin therapy offers the following advantages:

(1) It provides a predictable rate of fall of blood glucose.

(2) It is safe and rarely causes hypoglycemia, hypokalemia or sudden osmotic dysequilibrium leading to cerebral edema.

(3) Previous insulin therapy does not affect the response nor does the degree of acidemia.

(4) Insulin resistance is not much of a problem.

(5) Abrupt cessation of the drip corrects any hypoglycemia, should it develop during the infusion.

(6) It has sound pharmacokinetic basis.

(7) It is simple to use and can be administered by trained nursing personnel.

(8) The same insulin regime can be used to treat hyperglycemic, hyperosmolar non-ketotic diabetic coma..

The problem of possible adsorption of insulin to the glass bottle and the tubing can be overcome by addition of albumin to the infusate. In actual practice, little difference is observed whether one uses an isotonic saline solution or an albumin solution. However, it must be emphasized that insulin infusion is not a panacea and does not replace the vigilant physician in the management of diabetic coma.

Operationally, after an initial i.v. bolus of 10-15 units, insulin infusion may be used as follows: add 100-120 units of soluble insulin to 1000 ml of isotonic saline solution. Start a drip through a pediatric scalp vein set, the needle being inserted into a forearm vein (not the antecubital vein as this immobilises the elbow). Infuse at the rate of 40-50 ml/hour (10 drops/minute). This works out to 5-6 units/hour. Taking into account the adsorption of insulin to the glass and the tubing, the effective rate of delivery may be 3-4 units per hour. Reduce the rate by 50% or give insulin subcutaneously 4-6 hourly once blood glucose comes down to 250 mg%. If the blood glucose does not come down significantly within 4 hours of starting the infusion, double the drip rate.

If intravenous infusion of insulin is not possible for some reason, similar good results can be obtained by giving soluble insulin *intramuscularly* in the dose of 20 units initially, followed by 5 units once every hour. Subcutaneous insulin has a longer local t/2 of about four hours and may take too long to achieve effective concentration. When intramuscular route is used, rehydration becomes critical, particularly if the patient is also hypotensive. Usually one litre of isotonic saline given rapidly followed by another litre in one hour is advised, initially. Insulin injections should be given preferably into the deltoid.

(2) *Fluids*: One litre of normal saline is given during first half hour. The patient should then receive 0.45 per cent sodium chloride solution and a total 4 litres of fluid should be given by the end of 4 hours. Administration of half normal sodium chloride prevents the danger of hyperchloremic acidosis which would occur with normal saline in the presence of renal impairment. If circulatory failure exists, dextran or plasma may be used in addition but catecholamines should be avoided, if possible. When blood sugar starts approaching 300 mg. per cent, 5 per cent glucose is substituted. Care should be taken to prevent overloading the circulation in aged patients, which is more likely to happen in the latter part of the therapy, after correction of dehydration.

(3) *Acidosis*, if severe, may be corrected by intravenous administration of sodium bicarbonate solution (see Chapter 33).

(4) *Presence of infection* is carefully

looked for and treated with antibiotics. Routine administration of antibiotics prophylactically is, however, not recommended.

(5) *Potassium chloride* 2 g. is administered orally when the blood sugar has started approaching 300 mg. per cent and is repeated every 4-6 hours for the next 24 hours. This is necessary because, during recovery, plasma potassium shifts into the cell, causing hypokalemia.

(6) *Catheterization* of bladder should be avoided for fear of introducing infection. Gastric intubation is sometimes recommended but is potentially hazardous in an unconscious patient and should be avoided. After second day of the recovery, the patient should return to his normal food and insulin regime.

(B) **Hyperglycemic, hyperosmolar, nonketotic coma:**

This is an uncommon form of metabolic coma which occurs in diabetics who have just enough (exogenous or endogenous) insulin to prevent ketosis but not hyper glycemia. The blood sugar level is generally in excess of 1000 mg. per cent and may be as high as 2700 mg.%. Dehydration is severe. The treatment is similar to that of diabetic coma except that 0.45% sodium chloride solution is required in very large quantities.

GLUCAGON: Glucagon is a single-chain polypeptide made of 29 amino acids and with a molecular weight of 3485. Its amino acid sequence is known and it has been synthesized in the laboratory. It is synthesized, stored and secreted by the alpha cells of the islets of Langerhans. Enteroglucagon, a substance with glucagon like properties, has been isolated from the wall of the small intestine.

Glucagon is secreted in response to a fall in blood glucose level and a rise of plasma amino acid level. Surprisingly, a glucagon like substance is found in plasma even after glucose ingestion but not after intravenous glucose. It has been suggested that the ingested glucose liberates gut hormones into the circulation, and that of these, pancreozymine stimulates glucagon secretion from the alpha cells.

Actions of glucagon: Glucagon is the most potent glycogenolytic hormone known and produces a rapid rise in blood glucose by accelerating the hepatic phosphorylase via cyclic AMP. It stimulates neoglucogenesis only in the presence of glucocorticoids and stimulates lipolysis in the peripheral tissues, which, in turn stimulates ketogenesis.

Paradoxically, glucagon stimulates secretion of insulin from the beta cells in man and it has been proposed that it is involved in the secretion of insulin after ingestion of glucose.

Glucagon has also been demonstrated to have a significant myocardiac stimulant activity.

Absorption, fate and excretion: Given orally, it is destroyed by proteolytic enzymes. After parenteral administration, it is absorbed rapidly but has a short plasma half life. It is degraded mainly in the liver and kidneys.

Preparations and dosage: Glucagon injection USP is available as glucagon hydrochloride, in ampoules containing 1 and 10 mg. of the dry powder. Dose: 1 mg. subcutaneously or intravenously.

Therapeutic uses: (1) Glucagon is used for treating insulin hypoglycemia. If an intramuscular injection of 1 mg. of glucagon hydrochloride does not restore consciousness, a similar dose should be injected intravenously.

(2) It has been used in the diagnosis of insulinoma because of its insulin releasing property and in the diagnosis of pheochromocytoma because of its catecholamine releasing property.

(3) It has been used to diagnose the hepatic form of glycogen storage disease in which it fails to raise the blood sugar level on intravenous injection.

DIAZOXIDE: This benzothiadiazine analogue is a potent hyperglycemic agent. It is effective on oral administration and its effects are reversible on stopping therapy. It acts in three ways: (1) It inhibits the insulin release from the beta-cells of the normal and neoplastic pancreas by an alpha-adrenergic mechanism. This action is prevented by phentolamine and is reversed by sulfonylureas. (2) It stimulates release of catecholamines from the adrenal medulla. The latter inhibit insulin release by beta cells. (3) It increases the glucose output by the liver probably through a beta-adrenergic mechanism.

The important adverse effects are water retention with edema, hirsutism and with high doses nausea and vomiting.

It is given in a single, daily oral dose of 100-200 mg; it may be raised to 800 mg. A thiazide diuretic is commonly given along with it to prevent edema.

It has been found to be useful in the treatment of a wide variety of resistant hypoglycemias including those due to pancreatic insulinoma, glycogen storage disease and leucine sensitive hypoglycemia. Its use in hypertension is discussed in Chapter 26.

ORAL ANTI-DIABETIC AGENTS

Oral anti-diabetics must be distinguished from mere hypoglycemic drugs such as salicylates which are too toxic for clinical use in doses that effectively lower the blood sugar. An ideal antidiabetic drug (a) should be effective by mouth, (b) should be non-toxic and (c) should correct the basic metabolic defects in a diabetic, in addition to lowering of the blood sugar. Although the drugs available at present do not meet these requirements fully, they are useful for controlling diabetes mellitus in a selected group of patients.

The currently available oral antidiabetic drugs belong to two chemical classes (1) sulfonylureas and (2) biguanides.

SULFONYLUREAS: These compounds are chemically related to sulfonamides and have a basic structure as follows:

$$R_1\text{—}SO_2.NH.CO.NH\text{—}R_2$$

Fig. 59.4: General structure of sulfonylureas.

Pharmacological actions: Given orally or parenterally, these drugs lower the blood sugar level in non-diabetic as well as in selected diabetic individuals.

In diabetics, their first action is to lower the elevated plasma free fatty acid levels and this occurs even before the blood sugar is lowered. They are effective only in the presence of a functioning pancreas. When effective, they normalize the metabolic status of the diabetic patient in addition to lowering of blood sugar. Reports on their abilities to normalize elevated serum cholesterol and triglyceride levels are contradictory. As with insulin and unlike with biguanides, patients on sulfonylureas tend to gain weight while on therapy.

Mechanism of action:

(1) *Pancreas*: Sulfonylureas stimulate the release of insulin by the beta cells of the islets of Langerhans. A single dose causes a rise in the insulin level in the pancreatic vein and a smaller rise in the peripheral arterial blood. During the early days of sulfonylurea therapy IRI levels in response to a glucose load are high. During their chronic administration, the IRI levels return to normal despite continued control of hyperglycemia. During their prolonged use, they stimulate the proliferation of the islet cells in laboratory animals.

Certain differences, however, exist between effects of sulfonylureas and subcutaneously injected insulin. It must be remembered that sulfonylureas release insulin slowly and for prolonged periods into the portal circulation where its primary action is on the liver, in contrast to subcutaneously injected insulin which directly enters the systemic circulation.

(2) *Liver*: Sulfonylureas inhibit neoglucogenesis and glycogenolysis. Whether this is a direct action of sulfonylureas on the liver or whether it is due to a normalization of the intrahepatic enzyme pattern induced

by the early hyperinsulinemia caused by the drug is not clear. The liver is able to pour out less glucose in response to sulfonylurea-induced hypoglycemia than that in response to insulin. However, the hepatic glycogen stores are increased during sulfonylurea therapy.

The exact cause for continued control of hyperglycemia with normal IRI levels during chronic administration is unknown. But it may be due to either (a) improved sensitivity of beta cells to rising blood glucose level with more appropriate insulin secretion; or (b) the possible direct hepatic action mentioned above.

(3) In enormous doses, which can never be achieved clinically, sulfonylureas decrease the rate of insulin degradation. They, however, do not directly stimulate the peripheral utilization of glucose.

The basic action of all the sulfonylureas is similar. The various compounds differ from one another in their rate of absorption, metabolic fate, excretion and hypoglycemic activity of their metabolites, all of which decide their biological half life.

Absorption, fate and excretion: Sulfonylureas are rapidly absorbed from the gastrointestinal tract. They appear in the blood within 1-2 hours of their ingestion and peak plasma levels are achieved in 4-6 hours. They are partially protein bound in the plasma and are mainly metabolized in the liver (Table 59.2). The excretory product of tolbutamide in urine gives a false positive test for albuminuria with sulfosalicylic acid. Chlorpropamide is excreted unchanged in the urine. Because of its long half-life, 7-10 days are required for it to achieve plateau plasma levels. Hence, dose should not be increased more often than once in 10 days. Further, the drug should be used carefully in patients with chronic renal disease.

Adverse reactions: Considering the number of diabetics taking sulfonylureas, the toxicity of these compounds is remarkably low. The important toxic effects are as follows:

(1) Hypoglycemia can be precipitated by an excessive dose, decreased food intake, vomiting or by associated liver and kidney disease. Certain drugs like oral anticoagulants, sulphaphenazole, phenylbutazone and salicylates, potentiate the hypoglycemic effect of sulfonylureas by displacing them from protein binding. MAO inhibitors and propranolol produce a state of 'hypoglycemia unresponsiveness' and their combination with sulfonylureas or insulin can be dangerous. Alcohol may produce severe flushing in many and dangerous hypoglycemia in a few of the patients on sulfonylureas and hence should be avoided. Chlorpropamide induced hypoglycemia is rather resistant to treat-

Table 59.2: **The Sulfonylurea Compounds**

Drug	Plasma half life (hours)	Duration of action (hours)	Activity of metabolites	Daily dose (g)	
				Average	Maximum
Tolbutamide (Rastinon) 0.5 and 1.0 g. tab.	4-5	6-12	Inactive	1.5	5.0
Chlorpropamide (Diabenese) 0.1 and 0.25 g tab.	35	Up to 60	—	0.25	0.5
Acetahexamide 0.5 g.	5-8	12-24	Hypo-glycemic	0.5	1.5
Tolazamide 0.1 and 0.25 g. tab.	7	10-14	Hypo-glycemic	0.25	1.0
Glibenclamide 5 mg. tab. (Daonil, Euglucon)	12	12-15	Inactive	0.005	0.02
Glymidine ** 0.5 g. tab.	4		Inactive	1.0	2.0

** A sulfapyrimidine with virtually no cross-reaction with sulfonylurea in regard to skin rashes.

ment and may need prolonged glucose infusion.

(2) Sulfonylureas sometimes give rise to allergic skin rashes and bone marrow depression with leucopenia, thrombocytopenia and agranulocytosis. Aplastic anemia is rare.

(3) Chlorpropamide has been reported to give rise to cholestatic jaundice and occasionally pulmonary eosinophilia.

(4) Sulfonylureas have been claimed to be goitrogenic.

(5) They sometimes potentiate and prolong the CNS effects of barbiturates and other sedative—hypnotics.

(6) By potentiating the action of circulating ADH on the renal tubules, chlorpropamide causes water retention. Hyponatremia has been reported in a proportion of patients on this drug.

(7) Cardiovascular complications: See later.

Preparations and dosage: These are shown in Table 59.2. Tolbutamide is also available as aqueous solution (1 g. in 10 ml, for intravenous injection.

Choice of the sulfonylurea preparation: Tolbutamide is a commonly used drug and is relatively non-toxic. But it has to be taken 2-3 times a day and if 3 g. per day are not effective in controlling diabetes, larger doses are not useful. Chlorpropamide controls diabetes in a single daily dose. Although doses larger than 500 mg. per day are pharmacologically more effective, they are not generally used because of a disproportionate rise in the incidence of adverse effects. Chlorpropamide is generally effective in 'primary and secondary failures' on tolbutamide therapy. Glibenclamide, the latest addition to this list, is effective in a single daily dose and is effective in patients who are not controlled by maximum doses of chlorpropamide. The incidence of hypoglycemic reactions, however, is likely to be higher with this drug than with other sulfonylureas and the tolerated dose varies over a wide range from 2.5 to 20 mg. per day. The drug must, therefore, be used extremely carefully. Flushing has been reported to occur when alcohol is taken after chlorpropamide, tolbutamide or acetohexamide.

Therapeutic uses:

(1) **Maturity onset type of diabetics** (fresh cases): Sulfonylureas are useful in treating symptomatic maturity onset type of diabetics who cannot be controlled by diet alone. Patients who satisfy the following requirement are likely to respond satisfactorily.

(a) obese, or at least not underweight, subjects aged 40 years or more at the time of diagnosis,

(b) diabetes of less than 10 years duration, without significant ketonuria in the absence of an acute complication,

(c) fasting blood sugar less than 300 mg per cent,

(d) plain insulin requirements less than 40 units per day,

(e) absence of an acute complication (infection or surgery) likely to lead to ketoacidosis, of congestive cardiac failure and of severe renal disease.

Out of those selected carefully on the basis of the above criteria, about 70 per cent show satisfactory response to sulfonylureas. The remaining are termed 'primary failures'.

Therapy is started with either tolbutamide or chlorpropamide, depending upon the severity of the disease. The other drugs have no special advantages over tolbutamide and chlorpropamide. After the initiation of therapy, it may take 1-2 weeks to achieve an adequate and stable control and hence, the dose should not be increased at shorter intervals than this. If a patient is not controlled with tolbutamide, he may be changed over to chlorpropamide or a biguanide added to the therapy. Chlorpropamide failures should be given a trial with glibenclamide.

Of the patients who are initially well controlled with sulfonylureas, 5-25% (in different series) escape from this control every year. This is called 'secondary failure'. The important causes of secondary failure are progressive deterioration of patients' own pancreatic function, dietary excess, intercurrent disease, inadequate dose or failure to take the drug regularly. This can be treated by (a) changing over to another sulfonylurea, (b) addition of a biguanide or (c) starting insulin. After a few weeks of insulin, responsiveness to sulfonylureas sometimes returns spontaneously.

If a maturity onset diabetic well controlled by less than 20 units of insulin wishes to change over to oral therapy, insulin can be stopped abruptly and a sulfonylurea introduced. However, if the insulin requirement is between 20 and 40 units daily, the dose of insulin is progressively reduced while that of a sulfonylurea is progressively increased, till the latter completely takes over.

Such changeover from insulin to oral drugs should, however, be done only infrequently as repeated cessation and restarting of insulin therapy can encourage the development of antibodies to insulin and insulin resistance.

Whether asymptomatic maturity onset diabetics should receive long-term sulfonylurea treatment is uncertain. They probably would do as well (or perhaps better, in the light of the recent U.G.D.P. report) with diet, exercise and weight reduction alone. In such patients, improved carbohydrate tolerance might reflect spontaneous fluctuations in carbohydrate tolerance rather than any specific beneficial effect of the drug. Such spontaneous fluctuations are known to occur in the course of diabetes.

(2) **Pregnant diabetics:** A number of reports now indicate that sulfonylureas may be safely used to treat *mild* diabetes during pregnancy. When a potent and long acting drug such as chlorpropamide is used, it should be omitted on the day of the delivery and the newborn baby carefully watched for possible hypoglycemia.

(3) **Insulin resistant diabetes:** This has already been discussed.

(4) **Intravenous tolbutamide** has been used in the diagnosis of diabetes mellitus and of insulinoma and in predicting whether a newly diagnosed diabetic is likely to respond to sulfonylurea therapy.

(5) Chlorpropamide has been successfully used in diabetes insipidus.

Limitations of sulfonylureas: These drugs are ineffective in juvenile diabetics, very long standing diabetes of maturity-onset type and in diabetics whose disease is due to pancreatectomy or destruction of the pancreas by disease and in diabetic coma. Nor are they useful in the presence of ketosis, infection and during severe stress like operation.

BIGUANIDES: The general chemical structure of biguanides is as follows:

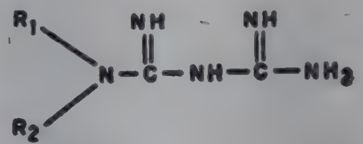


Fig. 59.5: General structure of Biguanides.

Pharmacological actions: In contrast to sulfonylureas, these agents do not lower the blood sugar in normal subjects but they do so in all types of diabetes mellitus. They potentiate the hypoglycemic action of insulin and sulfonylureas but by themselves they do not produce clinical hypoglycemia in diabetics.

Although they lower the blood sugar in diabetes, unlike insulin they do not inhibit ketogenesis in the liver. *Hence, diabetics on phenformin may develop ketoacidosis with minimum hyperglycemia and glycosuria.* Further, unlike insulin and sulfonylureas, biguanides decrease the glycogen content of the liver. Finally, unlike insulin they inhibit lipogenesis but not lipolysis in the adipose tissue.

They have been claimed to increase the fibrinolytic activity of plasma.

Mechanism of action: The exact mechanism of action of biguanides is not known. But the presence of either exogenous or endogenous insulin is probably necessary for their action. They do not stimulate insulin release from the pancreas. In fact, patients on biguanides show a less marked rise in plasma insulin level in response to a glucose load.

They stimulate the peripheral utilization of glucose. The exact mechanism of this action is not known. It has been proposed that biguanide induced inhibition of aerobic glycolysis stimulates anerobic glycolysis with resultant increased glucose uptake by the cells. Absolute confirmation of this hypothesis is still lacking. Biguanides inhibit hepatic neoglucogenesis. Lastly, they reduce glucose absorption from the intestines. This may be important in their euglycemic action because although oral GTT improves on biguanides, intravenous GTT does not.

Absorption, fate and excretion: Phenformin and metformin are rapidly absorbed from the gastrointestinal tract and give adequate plasma levels; phenformin in the form of special 'time disintegrating' (TD) capsules is absorbed more slowly and a single dose exerts more sustained action.

Phenformin is 1/3rd metabolized to inactive compounds and 2/3rds excreted unchanged in urine while metformin is largely excreted unchanged in urine. The dosage for metformin is almost 10 times that of phenformin and it has a longer duration of action.

Adverse reactions: Biguanides commonly produce an unpleasant, bitter or metallic taste, anorexia, nausea, and abdominal discomfort. This can be minimized by starting with a small dose and giving it with, rather than before meals. The time disintegrating capsule is tolerated better than tablets by many patients. They also produce lethargy, muscular weakness and an excessive weight loss in some patients. Rarely, anaphylactic shock or generalised urticaria can occur. Phenformin has also been reported to cause malabsorption of vitamin B_{12} and to interfere with hydrogen ion excretion by the kidneys.

In patients taking phenformin, the plasma levels of lactate are slightly elevated; if the patient has liver, heart or kidney disease, they tend to be significantly elevated. Should such a patient get an acute illness e.g. a severe infection, dangerous and potentially lethal lactic acidosis can easily develop. Hence, the use of phenformin is contraindicated in the presence of liver or kidney disease and in the presence of cardiac disease if congestive heart failure is also present. Further, even in otherwise normal diabetics doses of phenformin over 100 mg/day should be avoided.

Preparations and dosage:

(i) Phenformin 25 mg. tablets and 50 mg. T.D. capsules. Dose: 75 mg. daily maximum upto 200 mg.

(ii) Metformin 500 mg. tablets. Dose: 1500 mg. daily, maximum upto 4000 mg.

Therapeutic uses: Biguanides are helpful in the management of all types of diabetics. Their main uses are:

(1) Obese, maturity-onset diabetics who could be controlled with diet alone but find this therapy unacceptable. In such patients, the anorectic action of biguanides is of additional help in making the patients lose weight. Phenformin may be started in the dose of 25 mg. with each major meal, and increased gradually. Alternatively, one T.D. capsule may be given with breakfast daily.

(2) Biguanides may be added to a sulfonylurea in cases of primary or secondary failure (see above).

(3) In brittle juvenile diabetics, who have marked fluctuations of blood glucose levels, addition of a biguanide to insulin often helps to smoothen the control of these patients. However, biguanides cannot be used by themselves in treating juvenile diabetes.

(4) Phenformin has been used to treat mild diabetes during pregnancy.

(5) In non-diabetic obese persons (see Chapter 35).

When diabetics who are controlled with oral hypoglycemic drugs come to major surgery, they have to be given insulin.

Table 59.3 gives the approximate insulin equivalents of the oral drug regimes.

Table 59.3: Approximate Insulin Equivalents of Oral Hypoglycemic Drugs (After Ellenberg and Rifkin)

Oral drug	Dose (mg/day)	Insulin equivalent (u./day)
Tolbutamide	1500	15
	3000	30
Phenformin	Upto 100	15
	Over 100	35
Chlorpropamide	250	25
	500	50
Chlorpropamide + Phenformin	250 + 50	30
	500 + 100	50-60

U.G.D.P. report: A prolonged, multicentric study (called University Group Diabetic Programme) on the value of diabetic control in the prevention of degenerative vascular disease showed some unexpected results. These workers reported that morbidity and mortality from vascular disease was higher in patients treated with tolbutamide or phenformin than in those treated with diet alone or with diet + insulin. This report has not been universally accepted but the American Diabetic Association has recommended that "oral hypoglycemic agents should not be used in the management of prediabetes, latent or suspected diabetes or in the management of diabetics who can be controlled by diet; their use should be restricted to those who are poorly controlled on diet and are not able or willing to take insulin". At present, the shortage and the expense of insulin therapy, may preclude unqualified acceptance of these recommendations in economically poor countries like India.

Insulin substitutes: From time to time, claims are made about the indigenous preparations derived from plants or metals, found to possess hypoglycemic action in experimental diabetes. Such reports need critical evaluation prior to their clinical application. As hyperglycemia and glycosuria are prominent manifestations of diabetes mellitus, a new potential antidiabetic agent is usually tested for its ability to correct these abnormalities. It must be emphasized, however, that diabetes is not synonymous with hyperglycemia and glycosuria. It is a disease due to deranged total energy metabolism and the new drug must help to correct the fundamental defects in metabolism. While accepting such an agent, therefore, one should know the mechanism of its hypoglycemic action and also the possible long term effects. Otherwise, it is difficult to justify its use in place of established remedies which are shown to prevent the complications which is the major problem of diabetics today. Using a drug simply to lower the blood sugar level is like applying a dye to the hair "which though helps one to look younger, does not reverse the fundamental process of senescence".

SWEETENING AGENTS

These are non-carbohydrate substances devoid of food value, useful as sugar substitutes in diet and beverages. The compounds available are:

(i) SACCHARIN: This is a white crystalline powder, sparingly soluble in water, with marked sweetening properties. It is commonly employed as the sodium salt which is comparatively free from the unpleasant after-taste of saccharin. The salt has also been employed for measurement of circulation time.

Continued use of saccharin in small amounts has been shown to be harmless.

Saccharin tablet N.F. contains 12 mg. of saccharin. One tablet is approximately equivalent to 1 teaspoonful of sugar (7.5 g. sucrose). The sodium salt is available as 15, 30 and 60 mg. tablets and as a liquid preparation containing 250 mg. of saccharin sodium per ml.

(ii) SODIUM CYCLAMATE: This is a white, crystalline powder, soluble in water, with 30 times the sweetening power of sucrose and less bitter after-taste than saccharin. It has been in use as a food additive for the last 20 years without apparent ill effects. A recent report that the implantation of pellets containing cyclamate into the bladder of mice resulted in the appearance of malignant tumours of the bladder epithelium, led to its ban as food additive in U.S.A. and India. The evidence presented is, however, controversial and needs further confirmation. An excessive intake has a laxative effect. Calcium cyclamate is preferred in patients whose sodium intake needs restriction.

A mixture of equal quantities of sodium cyclamate and saccharin sodium is sweeter than would be expected from the sum of the sucrose equivalents of the two components and the bitter after-taste is noticeable only at a higher concentration than that with each component separately.

Saccharin and cyclamate sodium tablet N.F. contains 5 mg. of saccharin sodium and 50 mg. of cyclamate sodium.

Saccharin and cyclamate sodium solution N.F. contains 0.6% of saccharin and 6% of cyclamate sodium.

60 Adrenal Cortical Steroids

The importance of the adrenal cortex in the body economy has been realized only for the last 100 years or so. Thomas Addison's publication (1855) on the clinical picture of adrenal destruction focussed the attention of physiologists on the adrenal cortex. Subsequent experiments of Brown Sequard (1856) established that the adrenal gland was necessary for life. It took the next sixty years to prove that the cortex rather than the medulla was essential to life. From among the numerous crystalline steroids isolated from the adrenal cortex, hydrocortisone, cortisone, corticosterone, desoxycorticosterone, dehydrocortisol and aldosterone were shown to be biologically active. In the meanwhile, adrenocorticotropin (ACTH) or corticotropin, isolated from the adenohypophysis (1943), was shown to be responsible for the structural and functional integrity of the adrenal cortex. The phenomenal work by Hans Selye, who postulated the relationship of the adrenal cortex and stress, stimulated extensive work in adrenal physiology. Observation of the relief of symptoms of rheumatoid arthritis during pregnancy led to the use of cortisone in the treatment of this condition by Hench who was awarded the Nobel prize in medicine, jointly with Kendall and Reichstein whose work led to the synthesis of the steroid.

The adrenals consist of an outer cortex and an inner medulla, which are structurally and functionally different from each other. Accessory adrenal tissue is found at other sites in about 20 per cent of the individuals. During the foetal life the adrenal glands are larger than the kidneys; at birth they are about 1/3rd the size of the kidneys while in adults they weigh only 5-15 g.

Structurally and functionally, the adrenal cortex consists of three identifiable zones. From without inwards, they are zona glomerulosa, zona fasciculata and zona reticularis.

Pituitary-adrenal relationship: The specific adenohypophyseal hormone which maintains the structure and regulates the function of the adrenal cortex is ACTH. It is secreted by the basophil cells of the adenohypophysis and is a polypeptide with 39 aminoacids in a known sequence. The first 24 aminoacids which determine its biological activity are common to the hormone obtained from cattle, pig, sheep and man. The arrangement of the remaining 15 aminoacids shows species variations and is responsible for the antigenicity of the natural ACTH (corticotrophin) molecule. Its molecular weight is 4500. MSH (melanocyte stimulating hormone) of the anterior pituitary, has a sequence of amino acids identical with that of the first 13 of ACTH.

ADRENOCORTICOTROPIN

Regulation of ACTH release: A corticotropin releasing substance (CRF) is formed by hypothalamus and reaches the anterior pituitary by the portal circulation. It stimulates the release of ACTH. 5HT probably plays an important role in the release of ACTH. 5HT-antagonist cyproheptadine is known to inhibit the normal rise of plasma cortisol following insulin induced hypoglycemia. Further, oral administration of this drug (8-12 mg daily for 5 days) causes a significant depression in the plasma cortisol (hydrocortisone) level. Diurnal fluctuations in the rate of release of ACTH (dependent on similar diurnal fluctuations in CRF release) regulate the rates of secretion of hydrocortisone (cortisol) and corticosterone. The plasma level of hydrocortisone modulates the rate of release of CRF and in turn that of ACTH. Thus, increased plasma level of hydrocortisone inhibits ACTH release and reduces the ACTH store of the adenohypophysis. The newer synthetic corticosteriods have a similar but more prolonged inhibitory action. Decreased plasma level of hydrocortisone, as in Addison's disease and during metopirone administration, stimulates ACTH secretion, via the hypothalamus. This delicately balanced negative feedback mechanism adjusts the plasma level of hydrocortisone to within normal limits in healthy animals. In addition, under stressful situations, neuronal impulses from higher centres stimulate a release of CRF which ultimately elevates the output of hydrocortisone to meet the increased demands of the body. This important homeostatic mechanism which overrides the diurnal variations in ACTH secretion as well as its regulation by plasma cortisol level is deranged in various disease states such as primary adrenal disease, disease or destruction of the anterior pituitary and functional suppression of the hypothalamo-hypophyseal complex by corticosteroid administration.

Plasma ACTH levels undergo diurnal fluctuations resulting in fluctuations in the adrenocortical activity. The rate of secretion of hydrocortisone is maximum in the early hours of the morning, declines during the day and reaches a minimum at about midnight, the plasma level being highest at about 6 A.M. This 24 hours rhythmic secretion of ACTH and cortisol appears to be related to the sleep pattern and be modified by alterations in the latter.

Pharmacological actions of ACTH:

(a) **On the adrenal cortex:** ACTH stimulates the adrenal cortex to synthesize and secrete hydrocortisone, corticosterone, aldosterone and a number of weakly androgenic steroids. In hypophysectomised animals, the secretion of hydrocortisone is markedly depressed and does not rise in a normal fashion in response to 'stressful' stimuli. In the absence of adenohypophysis the adrenal cortex undergoes atrophy. Such atrophy can be prevented by the use of ACTH. The rate of secretion of aldosterone is, however, relatively unaffected after hypophysectomy.

ACTH reduces the cholesterol and ascorbic acid content of the adrenal cortex. The estimation of the latter forms the basis of a biossay for ACTH. The present evidence indicates that the hormone acts through the adenyl cyclase—cyclic AMP system. It acts at the level of conversion of cholesterol to pregnenolone (see later) which is the rate limiting step in the synthesis of adrenocortical steroids.

Prolonged administration of large doses of ACTH causes hyperplasia and hypertrophy of the adrenal cortex with increased secretion of hydrocortisone, corticosterone and weak androgens. The pharmacological actions of ACTH are in fact the pharmacological actions of these hormones, mainly hydrocortisone. These are discussed later. Gonadotropins do not have such stimulating effect on the adrenal androgens.

(b) **Extra-adrenal effects:** These are of relatively minor importance and include lipolysis in adipose tissue, ketosis, insulin resistance and cutaneous pigmentation.

Absorption, fate and excretion: ACTH is destroyed by proteolytic enzymes in the gut and hence, must be given parenterally. It is well absorbed after intramuscular injection but may also be given intravenously. Injected ACTH disappears rapidly from the blood with a half-life of about 15 minutes. It is rapidly metabolised and only a negligible amount appears in the urine. The quantitative response to a given dose of ACTH is greater (1) when it is given in the morning than in the evening and (2) when it acts slowly and for a longer period than when it acts rapidly and for a short period. The maximum adrenocortical stimulation is obtained in adults with 20 units of corticotrophin infused over 8 hours, 40 I.U. of depot corticotrophin given intramuscularly every 12 hours and by 1 mg. of depot synacthen given once a day.

Assay of ACTH: The older adrenal-cortical-ascorbic-acid-depletion assay has now been replaced by a sensitive radioimmunoassay.

Adverse reactions: Apart from the rare allergy, all other adverse actions of ACTH are due to increased secretion of adrenocorticosteroids and are discussed elsewhere.

Preparations and dosage:

(i) Corticotropin injection I.P. (ACTH injection): The solution should be freshly prepared before use. Dose: 20 units by slow intravenous infusion over 8 hours.

(ii) Corticotropin gelatin injection N.F. (ACTH depot injection) contains 40 units per ml. with suitably hydrolysed gelatin in water for injection. Dose: 40 units once daily in adults by intramuscular injection. It should not be injected intravenously.

(iii) Corticotropin zinc hydroxide injection B. P. is a sterile aqueous suspension containing 40 units of corticotropin per ml. with zinc hydroxide. Dose: initially 40 units daily intramuscularly; maintenance dose 20 units twice or thrice a week. Depot corticotropin preparations retain their biological activity upto 2 years if stored in a refrigerator but lose it in a few weeks at room temperature.

(iv) Synthetic ACTH preparation (Synacthen): This preparation, containing the first 24 of the 39 amino acids constituting natural ACTH, shows similar pharmacological actions as the natural product. The preparation does not evoke allergic reactions in individuals sensitive to natural ACTH, nor does it require a bioassay. The biological activity of 1 mg. is equal to 10 units of the natural preparation. It is administered by intravenous infusion in the dose of 0.25 mg. over a period of 4 to 8 hours. It should not be infused through blood or plasma as the enzymes present in blood tend to lyse the ACTH molecule. Synacthen depot preparation is also available. Its dose is 1 mg. intramuscularly every 48 hours.

Uses of ACTH:

(1) *Diagnostic*: ACTH can be used to demonstrate the integrity of the adrenal cortex. Except in patients with suppressed adrenal function, it increases the urinary excretion of 17-ketosteroids (17-KS) and 17-ketogenic steroids (17KGS) and plasma cortisol levels. This is of critical diagnostic value in Addison's disease. It has also been used to distinguish between adrenocortical hyperplasia and neoplasia as the cause of Cushing's syndrome.

(2) *Therapeutic*: (a) Most of the therapeutic uses of ACTH are identical with those of corticosteroids and are discussed later under glucocorticoids.

(b) ACTH is sometimes advocated to stimulate the adrenal cortex in patients on prolonged glucocorticoid therapy. This may, however, lead to a false sense of security. All patients who are on therapeutic doses of corticosteroids should be taken to have depressed pituitary-adrenal axis and treated as such in states of emergency and stress. Similarly, corticotrophin has been advocated after steroid withdrawal to restore the responsiveness of the adrenal cortex.

HORMONES OF THE ADRENAL CORTEX

The adrenal cortex elaborates three distinct groups of steroid hormones. The zona glomerulosa elaborates aldosterone and desoxycorticosterone (mineralocorticoids); zona fasciculata secretes cortisone and hydrocortisone (glucocorticoids); and the zona reticularis forms dehydroepiandrosterone and androstenedione (androgens) and traces of estrogens. Progesterone is synthesized as an intermediary in the synthesis of other steroids but is probably not secreted by the adrenal cortex into circulation.

Chemistry and synthesis: The adrenal cortical hormones are steroids (Fig. 60.1). The basic structure of a steroid is a com-

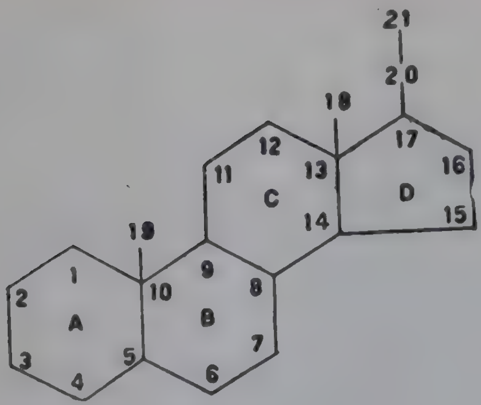


Fig. 60.1: Cyclopentanophenanthrene ring.

plex cyclopentanophenanthrene ring with various functional groupings (-H, $-CH_3$, -OH, = O) attached to different carbon atoms. All steroidal hormones have similar basic structure, with relatively minor differences which, however, cause striking alteration in their biological activity. They are sparingly soluble in water and, unlike peptide hormones, circulate in association with binding proteins. They are soluble in lipids and in various organic solvents. Their conjugates with glucuronic and sulfuric acids are, however, water soluble.

The Fig. 60.2 shows the outline of the three pathways of steroidal synthesis in the adrenal cortex. All the steroids are synthesized basically from 2-carbon acetate chains via cholesterol. Cholesterol is converted through pregenolone to progesterone. From here, the synthetic pathways for the three groups of hormones separate out. The physiologically important hormones secreted in significant quantities by the adrenal cortex are aldosterone, hydrocortisone, dehydroepiandrosterone and androstenedione. Hydrocortisone (cortisol), the important glucocorticoid in man, is interconvertible with cortisone. These steroids are secreted into the blood as they are formed and are not stored in the adrenal cortex in any significant quantities.

The various steps in the synthesis of

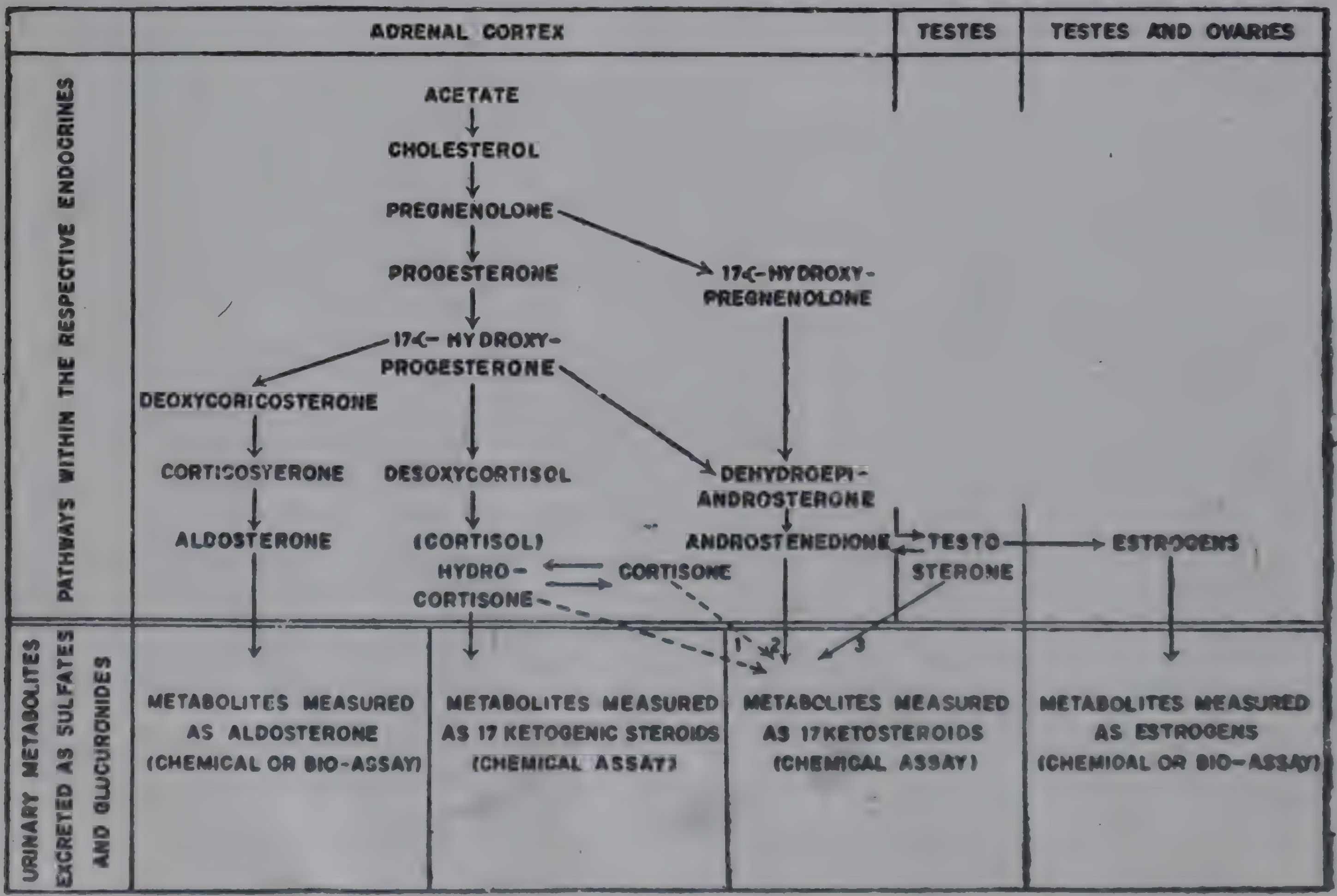

ADRENAL CORTEX
TESTES
TESTES AND OVARIES
PATHWAYS WITHIN THE RESPECTIVE ENDOCRINES
ACETATE
CHOLESTEROL
PREGNENOLONE
PROGESTERONE
17∝-HYDROXY-PREGNENOLONE
17∝-HYDROXY-PROGESTERONE
DEOXYCORICOSTERONE
CORTICOSYERONE
DESOXYCORTISOL
DEHYDROEPI-ANDROSTERONE
ALDOSTERONE
(CORTISOL) HYDRO-CORTISONE
CORTISONE
ANDROSTENEDIONE
TESTO-STERONE
ESTROGENS
1
2
3
URINARY METABOLITES EXCRETED AS SULFATES AND GLUCURONIDES
METABOLITES MEASURED AS ALDOSTERONE (CHEMICAL OR BIO-ASSAY)
METABOLITES MEASURED AS 17 KETOGENIC STEROIDS (CHEMICAL ASSAY)
METABOLITES MEASURED AS 17KETOSTEROIDS (CHEMICAL ASSAY)
METABOLITES MEASURED AS ESTROGENS (CHEMICAL OR BIO-ASSAY)

Fig. 60.2: Synthesis and metabolism of steroid hormones.
The broken arrows indicate that process 1 contributes very little to urinary 17 K.S., most of which come from processes 2 and 3.

these steroids are governed by specific enzymes. These enzymes, especially those concerned in synthesis of hydrocortisone, are sometimes congenitally deficient, leading to a deficiency of hydrocortisone.

Steroidal synthesis can be interfered with by (i) triparanol, which blocks the synthesis of cholesterol, (ii) metopirone, as discussed later and (iii) aminoglutethimide, which inhibits conversion of cholesterol to pregenolone.

Amphenone and o, p'-DDD cause necrosis of the adrenal cortex.

Table 60.1 shows the daily secretory rates of the important adrenocortical hormones. They are not stored in the adrenal cortex in significant quantities.

Table 60.1: **Secretory Rates of Cortical Hormones in Humans**

Hormone	Secretory rate (mg./day)
Hydrocortisone	8-25
Aldosterone	0.05-0.2
Corticosterone	2-4
Dehydroepiandrosterone (DHE)	15-30
Δ^4 Androstenedione	1-10

Regulation of the secretion of adrenal cortical hormones: The rates of secretion of the adreno-cortical hormones are regulated by the variations in the blood levels of ACTH. Nervous regulation plays no part in it. Although exogenously administered ACTH increases the secretion of aldosterone, physiologically, aldosterone output is independent of ACTH. This is shown by a relatively normal aldosterone output in hypopituitarism. Aldosterone secretion is mainly regulated by Angiotensin II, an octa-peptide derived from Angiotensin I, a decapeptide under the influence of a plasma 'converting enzyme'. Angiotensin I is derived from a plasma globulin in the presence of renin. Renin is released by the kidney when the renal arterial perfusion pressure is reduced for any reason such as vasoconstriction or reduced plasma volume. A reduction in sodium chloride intake is also a potent stimulus to aldosterone secretion while an increased intake of salt reduces its output. Changes in the intake of potassium have opposite but less marked effects on aldosterone output.

Metabolism and excretion of adrenal corticoids: The adrenal corticoids circulate in the plasma partly free and mostly bound to protein. The former is the biologically active form, the latter, a reserve form. Thus, when the total plasma cortisol level is 20 μg per 100 ml. almost 95% of this is bound to cortisol binding alpha-globulin (CBG, Transcortin) while free cortisol is only 1 μg per 100 ml. CBG gets completely saturated when the total plasma cortisol rises above this level. These steroids are metabolised in the liver and are excreted in the urine as conjugates of sulfuric and glucuronic acids. The corticosteroids being water insoluble, are excreted in the urine only in traces. The various urinary metabolites can be estimated as neutral 17-ketosteroids and 17-ketogenic steroids.

The term 17-ketosteroid denotes a steroid with a keto (=O) grouping attached to the 17th carbon atom (Fig. 60.1). 17-Ketosteroids can be estimated by a colour producing chemical reaction (Zimmerman reaction). Hence, 17-ketosteroid is a 'chemical concept' and not synonymous with 'androgens' which are biologically active masculinizing substances.

Neutral 17-ketosteroids measured in the urine comprise of:

(a) the weak adrenal androgens, dehydroepiandrosterone and androstenedione, and their metabolites; these form 2/3rds of the urinary neutral ketosteroids and are the only source in women,

(b) metabolites of testosterone; they make up the remaining 1/3rd of the urinary neutral 17-ketosteroids and

(c) some metabolites of hydrocortisone, which contribute very little to urinary 17-ketosteroids.

In normal adults the mean daily urinary output of 17-ketosteroids is 15 mg. in men and 10 mg. in women.

17-Ketogenic steroids are steroids which can be converted by chemical treatment to 17-ketosteroids. They are then measured as 17-ketosteroids but expressed as 17-ketogenic steroids. In health, the urinary 17-ketogenic steroids are all metabolites of hydrocortisone and cortisone. Hence, urinary 17-ketogenic steroid estimation serves as a valuable index of adrenocortical function. In health, the daily urinary output of 17-ketogenic steroids is 5-20 mg., being higher in heavier and lower in smaller individuals.

Aldosterone is excreted in urine partly as free aldosterone and partly as conjugates of tetrahydro-aldosterone.

GLUCOCORTICOIDS AND MINERALOCORTICOIDS

Adrenocorticoids exert a wide variety of physiological effects and pharmacological actions in the body. They also enable the organism to resist various types of noxious stimuli and environmental changes termed as 'stress'. The adrenal cortex is the organ, par excellence, of survival. In the absence of the adrenal cortex, survival is possible only under rigidly controlled and protected conditions wherein food and salt are available in plenty at all times and the environmental temperature is regulated. When exposed to 'stress', adrenalectomised animal dies quickly unless pretreated with corticosteroids.

The action of a given dose of a corticosteroid depends upon the environment and the condition of the organism. Under optimum conditions, a small dose of corticosteroids is sufficient to maintain an adrenalectomized animal in a state of well being. Under conditions of 'stress' it needs large doses of corticosteroids for survival, which if given to healthy animals, produce 'hypercorticism'.

Experimental evaluation of synthetic steroids: The easily quantifiable parameters of adreno-corticosteroidal activity are (a) sodium retention in adrenalectomized animals, (b) liver glycogen deposition, (c) suppression of hypothalamo-pituitary-adrenal axis, (d) anti-inflammatory action. The ability of a corticosteroid to maintain life in an adrenalectomized animal parallels its sodium retaining potency. On the other hand, the potencies based on suppression of hypothalamo-pituitary-adrenal axis, on liver glycogen deposition, anti-inflammatory action, work capacity of the skeletal muscles and involution of the lymphoid tissue parallel one another. There is however, in the case of many steroids, a complete dissociation between sodium retaining potency and liver glycogen deposition potency.

A corticosteroid with predominantly sodium retaining effects is called a *mineralocorticoid* e.g. aldosterone and desoxycorticosterone. A corticosteroid with predominantly liver glycogen depositing and neoglucogenetic actions is called a *glucocorticoid* e.g. hydrocortisone, cortisone and most of the newer synthetic steroids. Corticosterone, a natural corticosteroid and 9-alpha-fluorohydrocortisone, a synthetic steroid, have marked mineralocorticoid as well as glucocorticoid activities.

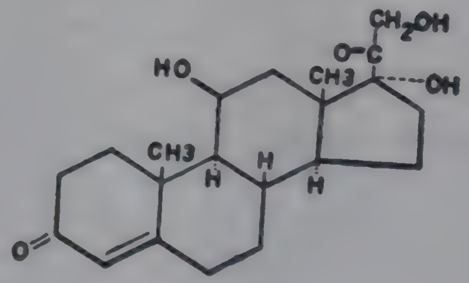


Fig. 60.3: Hydrocortisone.

Structure-activity relationship: The natural glucocorticoids like cortisone and hydrocortisone are pregnane derivatives with ketone groups at 3 and 20, a hydroxyl group at 21 and are unsaturated between carbon atoms 4 and 5. Compounds without oxygen at 11 position and hydroxyl group at 17 position have very weak glucocorticoid and anti-inflammatory properties. Introduction of an aldehyde group in the 18th position increases the mineralocorticoid potential tremendously, e.g. aldosterone. The anti-inflammatory and glucocorticoid potency is markedly increased by introduction of a double bond between 1 and 2 carbon atoms as in prednisone or prednisolone, by alpha-methylation in the 6 position as in 6 alpha methyl prednisolone and by 9 alpha fluorination and substitution at 16 position as in triamcinolone, dexamethasone and betamethasone.

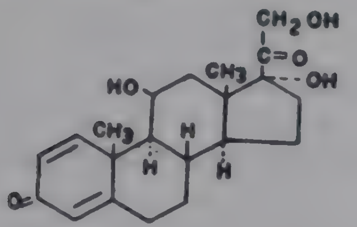


Fig. 60.4: Prednisolone.

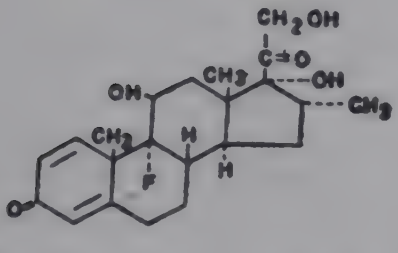


Fig. 60.5: Dexamethasone.

GLUCOCORTICOIDS: The important glucocorticoid secreted in man is hydrocortisone (cortisol). It possesses some mineralocorticoid activity too. Since some of the pharmacological actions of hydrocortisone are, in fact, its physiological actions, these are discussed together.

Pharmacological actions: Glucocorticoids exert a variety of physiological effects and pharmacological actions.

(1) **Metabolic effects:** The glucocorticoids affect the metabolism of carbohydrates, proteins, fats, electrolytes, water and calcium.

(a) *Carbohydrate and protein metabolism*: The important effects are inhibition of incorporation of amino acids into protein in the peripheral tissues (antianabolic action) and stimulation of their conversion into glucose (neo-glucogenesis) in the liver. The plasma amino acid level rises significantly. Simultaneously, the plasma glucagon level also rises markedly during chronic but not acute administration. During the process of neoglucogenesis the amino acids are deaminated and the nitrogen residue is excreted in urine. This accounts for such phenomena as, (i) inability of the adrenalectomized animal to maintain normal blood sugar level while fasting and the ability of glucocorticoids to correct this disability, (ii) the hyperglycemia and glycosuria induced by chronic administration of glucocorticoids in large doses and encountered in Cushing's syndrome. The protein antianabolic (rather than catabolic) effect accounts for wasting of muscles and thinness of the skin as seen in Cushing's syndrome. Glucocorticoids also inhibit peripheral glucose utilisation.

(b) *Fat metabolism*: Glucocorticoids play a 'permissive' role in the mobilization of fat from the peripheral fat depots by adrenaline and by growth hormone. Such mobilization is markedly inhibited in the total absence of glucocorticoids. Prolonged administration of excessive glucocorticoid causes a re-distribution of fat in the body, with a loss from the extremities and a deposition in the neck (buffalo hump), supraclavicular area and face (moon face). The mechanism of this re-distribution is not known. Plasma lipids are not changed consistently in either hypocorticism or hypercorticism.

(c) *Electrolytes and water metabolism*: Hydrocortisone has a feeble salt retaining and potassium wasting effect. However, when large doses (300 mg./24 hours) are used, sufficient salt retention occurs to make the concurrent use of a mineralocorticoid unnecessary. The details of the effects on electrolytes and water are discussed under mineralocorticoids. Under certain circumstances, the newer synthetic steroids, dexamethasone, betamethasone and triamcinolone, may actually produce a marked sodium loss in the urine.

Hydrocortisone is essential for excreting a water load. Adrenalectomized animals cannot excrete a water load and tend to develop water intoxication. This defect is corrected by administration of a glucocorticoid. The exact mechanism of this action is not known.

(d) *Calcium metabolism and bone*: In pharmacological doses, glucocorticoids antagonize the action of vitamin D on the gut and reduce absorption of calcium. Given in large doses for prolonged periods, they interfere with the development of cartilage and inhibit linear growth in children. As a result of the protein catabolic action, glucocorticoids inhibit formation of new bony tissue. Hence, the continuous resorption which occurs as a part of bone re-modelling leads to severe osteoporosis in chronic states of hypercorticism.

(2) **Cardiovascular system:** The important cardiovascular changes which occur in adrenal insufficiency are partly due to mineralocorticoid deficiency which acts through its effects on electrolyte and water metabolism and partly due to glucocorticoid deficiency. Usually the blood volume is reduced and blood viscosity is increased. These defects are only partially corrected by administration of sodium chloride and/or a mineralocorticoid. Addition of a glucocorticoid completely restores the circulation to normal. The absence of glucocorticoids leads to increase in capillary permeability, inadequate vasomotor responses of smaller blood vessels and reduction in the cardiac output. Glucocorticoids not only potentiate the pressor response of blood vessels to adrenaline and noradrenaline but also protect the blood vessels from the toxic effects of the latter. In pharmacological doses, they have a positive inotropic action on the heart.

Hypertension is sometimes seen during chronic administration of glucocorticoids and in patients with Cushing's syndrome. In the latter condition, it is an important cause of death.

(3) **Muscles:** Muscular weakness is a feature of Addison's disease. It is specifically corrected by a glucocorticoid. The weakness has been shown to be unrelated to abnormalities in electrolyte and carbohydrate metabolism; there is also no primary muscular or myoneural abnormality. The muscle weakness in adrenal insufficiency is largely due to inability of the circulatory system to respond to the stress of increased muscular activity.

The myopathy which is seen in hypercorticism is discussed later.

(4) **CNS:** Patients with Addison's disease show apathy, depression, irritability and sometimes psychosis. All these are corrected by administration of glucocorticoids.

Patients receiving large doses of glucocorticoids sometimes show mood elevation, euphoria, nervousness, restlessness and even psychosis. These are all reversible on stopping the therapy.

(5) **Hematological actions:** Hyperplasia of the lymphoid tissue and peripheral lymphocytosis are seen in Addison's disease while Cushing's syndrome is characterized by lymphocytopenia and dissolution of lymphatic masses in the body. ACTH or glucocorticoids cause a rapid lysis of lymphatic tissue and a lymphocytopenia with overall leucocytosis. These agents also cause a fall in the circulating eosinophils. The eosinopenia following ACTH administration was once used as a test of adrenal cortical response. A neutrophilia is seen during chronic administration of glucocorticoids. A mild secondary polycythemia is a characteristic feature of Cushing's syndrome.

(6) **G. I. tract:** Glucocorticoids increase both basal and nocturnal acid gastric secretion.

(7) **Mesenchymal tissue and anti-inflammatory action:** ACTH and glucocorticoids prevent or suppress the clinical features of inflammation such as local heat, redness, swelling and tenderness. At the tissue level, they suppress the early phenomena (edema, fibrin deposition, capillary dilatation, migration of phagocytes into the inflamed area and phagocytosis) as well as the late manifestations (capillary proliferation, fibroblastic proliferation, deposition of collagen and cicatrization). Fibrous tissue, once formed, is not dissolved by corticosteroids.

These anti-inflammatory effects are non-specific as the cause of the inflammatory reaction is not controlled by the corticosteroids. The anti-inflammatory effects are due to a local action of the steroids as they are equally well seen on topical application. In large doses they interfere with wound healing.

The anti-inflammatory actions of glucocorticoids are based on: (a) reducing the increased permeability of capillaries, (b) maintenance of the integrity of the cell membrane even in the presence of toxins and thus inhibiting cellular swelling, (c) stabilization of the lysosomes membranes. The lysosomes are tiny baglike intracellular organelles full of lytic enzymes which digest the cell contents if they (the enzymes) leak out of the lysosomes. Further, these enzymes—acid hydrolases—enhance and perpetuate the inflammatory response by attacking extracellular protein substituents, and (d) inhibiting lysosome release from granulocytes as well as inhibiting phagocytosis.

This anti-inflammatory effect of corticosteroids forms the basis for their clinical use in many different conditions.

(8) **Anti-allergic and anti-immunologic actions:** Thymus derived lymphocytes are highly susceptible to the actions of corticosteroids so that cell immune responses are modified following their administration. Corticosteroid thus, in large doses (40-60 mg. of prednisolone per day), can cause lysis of the T-cells, prevent homograft rejection and suppress cell-mediated hypersensitivity reaction. The corticosteroid doses that modify cell-mediated immunity do not suppress the humoral antibody production by B-lymphocytes.

The glucocorticoids also seem to inhibit phagocytosis of antigens and their subsequent intracellular digestion by the macrophages. Only enormous doses (150-200 mg. of prednisolone per day) of such steroids could alter gamma globulin production by the plasma cells in circulation. In spite of experimental evidence of glucocorticoid actions at many points in the immune response, clinically they are beneficial because of their outstanding potent anti-inflammatory property.

Although corticosteroids do not, in moderate doses, interfere with antibody production nor with antigen-antibody union or with the liberation of histamin from the tissues damaged by such union, they suppress the inflammatory response to it. This last action is important in the supression of such allergic phenomena as urticaria, allergic rhinitis and allergic bronchial asthma.

Clinically, corticosteroids modify the course of many diseases in which immune responses are believed to play a role. Although, they do not modify the basic disease process, they suppress the inflammatory response to injury. It must be noted that the glucocorticoids increase the susceptibility to a variety of bacterial fungal, viral and parasitic superinfection.

(9) **Miscellaneous actions:** Glucocorticoids have uricosuric and non-specific antipyretic effects. Their analgesic effect depends upon their anti-inflammatory action. Glucocorticoids markedly increase the activity of phenylethanolamine—N—methyltransferase, an enzyme located almost exclusively in the adrenal medulla and which catalyses the conversion of norepinephrine to epinephrine.

(10) **Inhibition of hypothalamo-hypophyseal axis:** Glucocorticoids given in large doses for longer than 1 week suppress the hypothalamohypophyseal-adrenal axis and cause adrenocortical atrophy. Such patients during therapy and for long periods (as long as 12 months) thereafter are unable to increase their endogenous output of hydrocortisone in response to stress. The secretion of ACTH by the pituitary gland usually returns to normal within 4-5 months but the ability of the adrenal cortex to respond adequately to endogenous ACTH may be impaired for upto 12 months after cessation of steroid therapy. Ultimate recovery of function, however, occurs in all the cases. Hence, it is important to enquire about past

administration of corticosteroids in all patients undergoing surgery or having an acute illness and to administer, if necessary, supportive doses of glucocorticoids.

Patients who are on small doses of any glucocorticoid (20 mg. of hydrocortisone or equivalent doses of other glucocorticoid per day) and those who are on high doses of intermediate acting glucocorticoids (see Table 60.2). *on alternate days* show little or no suppression of the hypothalamo-pituitary-adrenal axis as tested by response to an injection of a pyrogen. When large doses are used daily and for prolonged periods, the suppression is most marked when the entire daily dose is given at bed-time and is least when it is given on rising in the morning. Because of their very prolonged action, the long acting glucocorticoids are not suitable for alternate day administration but can be given once in 3 to 4 days to achieve the same results with minimal suppression. The other advantages of the alternate day therapy are the minimization of the nitrogen and calcium balance. It, therefore, permits safer administration of much larger total dosage of glucocorticoids. Hence, whenever possible, in patients requiring high-dose, prolonged glucocorticoid therapy, the alternate days program should be attempted.

The long acting compounds, however, are eminently suited for uniform and continuous suppression of ACTH secretion in the syndrome of congenital, virilizing, adrenocortical hyperplasia. As the peak secretion of ACTH occurs at night (in this condition as in normal persons), the entire daily dose of the long acting glucocorticoid should be given at bedtime.

After use for more than 7 days in high doses (see above) glucocorticoids should never be abruptly withdrawn as this may precipitate an acute adrenal insufficiency. Instead, the dose should be gradually tapered off, reducing it by 12-15 per cent every 4-5 days.

Absorption, fate and excretion: Hydro-

Table 60.2: Comparison of Various Glucocorticoids

Drug	Therapeutic efficacy	Glucocorticoid activity	Mineralocorticoid activity	Plasma half-life (minutes)	Half-time of glucocorticoid activity (hours)	Comparative doses *(mg.)
Short acting						
Cortisone	1	1	1	40	4-6	25
Hydrocortisone	1.25	1.25	1.25	80	8-12	20
Intermediate acting						
Prednisolone	4	4	0.0005	200	12-36	5
Methyl prednisolone	5	5	0	200	12-36	4
Triamcinolone	5	5	0	200	12-36	4
Long acting						
Dexamethasone	20	20	0	300	36-54	0.75
Betamethasone	20	20	0	300	36-54	0.75

* These dose relationships apply to oral and intravenous administration of these compounds but not to intramuscular or intra-articular administration of these compounds or their derivatives.

cortisone is rapidly and completely absorbed from the gastrointestinal tract. Absorption of aqueous suspension or of the acetate from intramuscular site is much slower and hence, the effect lasts much longer. The onset of action is, in fact, faster after oral than after intramuscular administration and the oral dose is about the same as the parenteral dose. Hemisuccinate of hydrocortisone is rapidly absorbed from the intramuscular site. Exogenous hydrocortisone is metabolised in the same way as the endogenous hydrocortisone.

Adverse reactions: The toxic effects of corticosteroids are related to individual susceptibility, dosage and duration of therapy. Single doses, however large, are harmless and may, therefore, be used without hesitation in situations where life is suspected to be threatened by a adrenocortical or pituitary insufficiency or by cerebral edema. Short term therapy (generally 1-2 weeks) with small or moderate doses is unlikely to produce any harmful effects. Prolonged therapy with corticosteroids in doses higher than 20-30 mg. of hydrocortisone or equivalent doses of other steroids per day is liable to cause adverse effects. Hence, this is the generally recommended maximum maintenance dose in prolonged glucocorticoid therapy. The only exception is life threatening conditions where doses large enough to suppress the clinical manifestations of the disease are needed and then one accepts adverse effects as the price one has to pay for keeping the patient alive.

The important adverse effects of glucocorticoid therapy are:

(a) **Gastrointestinal tract:** Acute erosive gastritis with hemorrhage may occur during intensive short-term therapy with glucocorticoids. Peptic ulceration is troublesome during prolonged therapy with both high and low doses. Intestinal perforation and pancreatitis are the other reported gastro-intestinal complications of such therapy.

(b) **Musculo-skeletal effects:** Proximal myopathy and osteoporosis with compression fractures of the vertebrae are serious complications. Rarely, acute aseptic necrosis of bone may occur.

(c) **Central nervous system:** Acute psychotic reactions may occur especially during intensive therapy. Benign intracranial hypertension and aggravation of epilepsy particularly in children are known to occur.

(d) **Eyes:** Glaucoma occurs in some patients during local glucocorticoid therapy and posterior subcapsular cataract has been reported during their systemic use especially in children with rheumatoid arthritis.

(e) **Cardio-vascular and renal system:** Hypertension, salt and water retention and rarely hypokalemic alkalosis can occur during this therapy but are uncommon with dexamethasone, betamethasone and triamcinolone.

(f) **Metabolic effects:** Clinical manifestations (including ketoacidosis and non-ketotic, hyperglycemic, hyperosmolar coma) of genetic diabetes mellitus can be precipitated. Pre-existing diabetes, however, is not an absolute contraindication to glucocorticoid therapy and development of glycosuria during therapy in itself does not warrant cessation of treatment. Some patients develop hyperlipidemia.

Prolonged therapy may cause central obesity with moon face and buffalo hump Pink florid striae are liable to appear on the abdomen, hips and pectoral regions and the skin may become friable. The patient is liable to get spontaneous ecchymosis and to bruise easily.

(g) **Endocrine system:** High-dose corticosteroid therapy abolishes the hypothalamic-pituitary-adrenal response to pyrogen stress, whereas low doses of steroid produce only insignificant alterations to the response to pyrogen stress. It is generally accepted that adrenal atrophy is apparent in nearly all species tested after 10 days of high-dose glucocorticoid therapy. Further such inhibition of the feedback response persists up to 12 months if corticosteroid levels are maintained in the supraphysiologic range for only two weeks. Abrupt withdrawal of glucocorticoids can, therefore, precipitate acute adrenocortical insufficiency (Withdrawal syndrome). Another type of withdrawal syndrome consists of fever, myalgia, arthralgia and malaise; it is difficult to distinguish it from a reactivation of the underlying disease such as rheumatoid arthritis and its mechanism is not known.

(h) **Retardation of linear growth** occurs in children who receive more than 50 mg. of cortisone per square meter of body surface area per day. In equivalent therapeutic doses prednisolone is twice and dexa- and beta-methasones are thrice as growth inhibiting as cortisone.

(i) **Suppression of inflammation and immune response:** Glucocorticoids may mask the important clinical features of a serious illness e.g. fever and abdominal rigidity may be absent when a patient on these drugs develops acute peritonitis, which may, therefore, be missed. Further, pre-existing infection like tuberculosis can spread and superinfection with other organisms like bacteria and fungi can occur.

(j) **Interaction with other drugs:** Glucocorticoids enhance the renal clearance of salicylates. Abrupt cessation of the former in a patient who is receiving both drugs may precipitate salicylate toxicity. On the other hand, drugs such as barbiturates increase the degradation of glucocorticoids by hepatic microsomal enzyme induction.

(k) **Miscellaneous changes:** These include hyper coagulability of blood with thrombo-embolic complications, hirsutism, loss of scalp hair, subcutaneous atrophy and delayed wound healing.

There are certain differences between the adverse effects of corticotrophin and glucocorticoids. With oral glucocorticoid therapy, dyspepsia, gastric complications, bruising, striae formation, loss of muscle mass and osteoporosis are more common. With corticotrophin, on the other hand, there is a higher incidence of hypertension, pigmentation, hirsutism and acne. In children, corticotrophin causes less interference with growth than the glucocorticoids. Suppression of the pituitary adrenal axis is less marked and shorter lived following cessation of corticotrophin than glucocorticoid therapy.

Newer synthetic glucocorticoids: Since cortisone and hydrocortisone were found to have many undesirable adverse effects, attempts were made to synthesize new steroid compounds with increased anti-inflammatory activity, preferably without the capacity to induce salt and water retention and other adverse effects. These synthetic glucocorticoids include prednisone, prednisolone, triamcinolone, paramethasone, dexamethasone, betamethasone and 6-methyl-prednisolone. As shown in Table 60.2 the last five newer synthetic steroids show negligible or almost absent mineralocorticoid activity. However, there is no convincing evidence that they are superior to prednisone and prednisolone with respect to the other adverse effects such as peptic ulceration, osteoporosis and glycosuria. All of them are potent pituitary inhibitors. In addition, triamcinolone has a great propensity to cause myopathy while the incidence of increased capillary fragility and ecchymosis is more with triamcinolone, dexamethasone and betamethasone.

The newer steroids have pharmacological actions and adverse effects identical with those of hydrocortisone except the mineralocorticoid actions. They are less extensively protein bound than hydrocortisone and hence diffuse more completely into the tissues than the latter. They are effective in smaller doses. Such smaller doses, however, should not be construed to give them any superiority over the older preparations as in equivalent therapeutic doses their adverse effects are similar. In certain special circumstances such as in adrenal suppression test, a steroid with a smaller effective dose (e.g. dexamethasone) is preferred to hydrocortisone because the former does not contribute to the urinary keto- and ketogenic steroids which are being measured. Another advantage of the newer steroids is that it has been possible to prepare a variety of their esters suitable for topical application and local injections into tissues.

The newer glucocorticoids are rapidly absorbed when given by mouth. Their long-acting esters, which are used for topical application and intra-articular injection, are poorly absorbed. They are metabolized like hydrocortisone by the liver but more slowly than the latter.

Preparations and dosage of glucocorticoids:

(a) **For systemic use:**

(i) Cortisone acetate, I.P. (Corlin) tablets, containing 25 mg. Dose: 50 to 400 mg. daily, in divided doses.

(ii) Cortisone injection I.P. is a suspension of cortisone acetate (25 mg. per ml.) in sodium chloride injection. Dose: 50 to 200 mg. daily intramuscularly in single or divided doses.

(iii) Hydrocortisone tablet N.F. contains 10 mg. of the drug, for dosage, see text.

(iv) Hydrocortisone hemisuccinate B. P. (Efcorlin) being readily water soluble is administered intramuscularly, by intravenous infusion or as a retention enema. Approximately 133 mg. of the salt contains 100 mg. of hydrocortisone. For retention enema, a dose equivalent to 100 mg. of hydrocortisone, dissolved in 120 ml. of normal saline is given each night.

(v) Prednisone tablet I.P. contains 5 mg. of the drug, either in the pure form or as an equivalent amount of prednisone acetate. Dose: 10 to 100 mg. daily in divided doses.

(vi) Prednisolone tablet, I.P. contains 5 mg. of the drug or an equivalent amount of prednisolone acetate. Dose: 10 to 100 mg. daily in divided doses.

(vii) Prednisolone acetate suspension contains 25 mg. per ml. It is administered by intramuscular, intra-articular or peri-articular injection.

(viii) Prednisolone or prednisone pediatric drops N.F. contain 5 mg. of prednisolone or prednisone per ml. Dose: newborn, 0.3 to 0.4 mg. per kg. per dose; infants, 0.2 to 0.3 mg. per kg. per dose; older children, 0.15 to 0.2 mg. per kg. per dose.

(ix) Prednisolone sodium phosphate B.P., in contrast to prednisolone or its acetate, is soluble in water. Approximately 27 mg. of the salt are equivalent to 20 mg. of prednisolone. Dose: equivalent to 20-100 mg. of prednisolone intravenously and 20 mg. by retention enema.

(x) Methylprednisolone B.P. 4 mg. tablets. Dose: 10 to 80 mg. daily in divided doses.

(xi) Methylprednisolone sodium succinate, unlike the parent compound, is water soluble. Dose: equivalent to 40 mg. of methylprednisolone base by intramuscular or intravenous injection; 40 to 120 mg. as a retention enema.

(xii) Triamcinolone tablet N.F. (Ledercort, Kenacort) contains 4 mg. of triamcinolone. Dose: 4 to 48 mg. daily in divided doses.

(xiii) Triamcinolone diacetate injection for intramuscular or intra-articular use. Dose: 5 to 40 mg. It must not be given intravenously.

(xiv) Paramethasone acetate tablets 1 and 2 mg., the daily dose: 2 to 4 mg.

(xv) Betamethasone tablet N.F. (Betnelan) contains 0.5 mg. of the drug. Dose: 0.5 to 5 mg. daily. For ulcerative colitis, 4 mg. twice daily in retention enema.

(xvi) Betamethasone sodium phosphate, a water soluble salt is available as tablets and for injection (Betnesol) nearly 1.3 mg. of the salt is equivalent to 1 mg. of betamethasone. Dose: equivalent to 0.5 to 5 mg. of betamethasone by mouth; for acute adrenal insufficiency, 10 to 80 mg. by intravenous or intramuscular injection daily, in divided doses.

(xvii) Dexamethasone tablet B.P. (Decadron) contains 0.5 mg. of the drug. Doses similar to betamethasone tablets.

(xviii) Dexamethasone 21-phosphate injection N.F. (Decadron injection) contains 4 mg. of the salt per ml. Roughly 1.3 mg. of the salt is equivalent to 1 mg. of the base. Dose: 4 to 20 mg. of the base by intramuscular or intravenous injection.

(b) **For topical use:** Numerous preparations containing either the glucocorticoids alone or in combination with antibiotics are available for topical therapy. The important preparations are: hydrocortisone eye ointment I.P., which contains 2.5 per cent w/v of hydrocortisone acetate; hydrocortisone eye drops N.F. 1 per cent; hydrocortisone lotion, 2.5 per cent and hydrocortisone acetate injection administered intra-articularly in the dose of 5 to 50 mg. Other preparations available for intra-articular injection include methyl prednisolone acetate, prednisolone pivalate, fluromethololone and flumethosone pivalate.

Many other preparations containing either prednisolone 0.5% or various newer steroids in concentration of 0.025-0.1% are available in the form of ointments, creams and eye drops, for local use. Some of these such as betamethasone, fluocinolone and clobetasone are very potent.

Therapeutic uses of glucocorticoids: These can be divided into:

(a) Substitution therapy.

(b) Pharmacological therapy.

(a) **Substitution therapy:** Addison's disease and hypopituitarism are indications for substitution therapy with glucocorticoids. They are discussed under mineralocorticoids.

(b) **Pharmacological therapy:** The indications for such therapy may be conveniently divided under several heads.

(1) *Intensive short term therapy* can save life and reduce morbidity in certain potentially lethal conditions in which the inflammatory or the metabolic response of the body itself threatens life. These conditions include: allergic emergencies such as status asthmaticus; anaphylactic shock; circulatory collapse unresponsive to pressor amines; acute necrotizing vasculitis; water intoxication; central hyperthermia; and acute hypercalcemia accompanying vitamin D intoxication or hormone therapy of metastatic breast cancer. In status asthmaticus, the glucocorticoids take several hours to act and their use supplements that of the bronchodilators. In circulatory failure, a single massive dose (preferably of a long acting compound) sometimes restores the blood pressure to normal. In hypercalcemic crisis, glucocorticoids take several days to reduce the plasma calcium and must be used along with other quicker acting measures. In all these conditions, large doses such as 100-200 mg. of prednisolone per day may have to be used but the therapy with such doses seldom lasts longer than 48-72 hours. In such cases, the adverse effects of glucocorticoids mainly consist of burning and itching at the mucocutaneous junctions, and rarely of multifocal ventricular premature beats, precipitation of ketoacidotic coma in a genetic diabetic and acute erosive gastritis with hemorrhage. With such short therapy, the dose of the glucocorticoid need not be tapered but the drug may be omitted abruptly.

(2) *Prolonged, high-dose, suppressive therapy* is indicated in acute rheumatic fever, ulcerative colitis, subacute hepatic necrosis, chronic active hepatitis, alcoholic hepatitis, autoimmune hemolytic anemia, idiopathic thrombocytopenic purpura, acute lymphatic leukemia, disseminated Hodgkin's disease, nephrotic syndrome, acute homograft rejection, pemphigus and collagen diseases. In these diseases, the initial dose may be as high as 100-200 mg. of prednisolone per day, the therapy continues longer than 7-10 days and the maintenance dose may be 15 mg of prednisolone or more per day. The fear of adverse reactions is utmost in this group and the patients need the closest supervision. A rapid reduction in the dose can cause an acute exacerbation of the disease being treated. On the other hand, abrupt cessation is dangerous and can precipitate acute adrenocortical insufficiency; the patients must be warned about this possibility. In order to minimise the suppression of the hypothalamo-pituitary-adrenal axis during such prolonged, high-dose therapy, the alternate day regime should be tried once the clinical improvement has stabilized; if it is unable to maintain the clinical remission, the entire daily dose may be given in the morning with the same objective in mind.

(3) *Low-dose, chronic, palliative the-*

rapy consists of the use of small doses of a glucocorticoid (2-10 mg. of prednisolone per day) as an adjunct to some other drug e.g. salicylates in rheumatoid arthritis. Here, total relief of symptoms is not aimed at in order to avoid the adverse effects of the glucocorticoid. Such low-dose therapy should not be tried on alternate days as it is ineffective in controlling the disease adequately. As the therapy is generally very prolonged, sometimes lifelong, the patients need close supervision. The dose of the glucocorticoid should be abruptly raised 2-4 times during such stress as surgery or a severe infection in such patients.

(4) *Chronic, suppression of pituitary ACTH secretion* is indicated in congenital, virilizing, adrenocortical hyperplasia. This is best achieved with the use of a long acting compound such as dexamethasone or betamethasone in the dose of 0.75 mg at bedtime daily. Such therapy suppresses the urinary 17-ketosteroids adequately and rarely causes any adverse effects. It must be impressed upon the parents of such a child that the therapy must continue lifelong.

(5) *Topical application* is found valuable in many dermatological, ocular and external ear conditions. Ocular conditions benefited by local corticosteroid therapy are interstitial keratitis, phlyctenular conjunctivitis, spring catarrh, iritis and iridocyclitis, whereas, posterior uveitis and sympathetic opthalmia need systemic medication.

Local steroid therapy is valuable in many inflammatory dermatoses and for controlling exacerbations of pruritic eczema, and psoriasis. They are not recommended for urticaria. Usually, for eczematous conditions, local use of 1% hydrocortisone ointment is all that is necessary. Unfortunately, steroid ointments are being misused as a dermatological panacea because they usually give dramatic relief in inflammatory and pruritic conditions of the skin. Their indiscriminate use, however, is not only wasteful but also harmful. Application of a steroid ointment for such conditions as herpes simplex, herpes zoster, ringworm and impetigo may lead to marked exacerbation of the disease. Corticosteroids accelerate the fungal growth and spread and cause local skin atrophy with resultant telangiectasia, purpura and striae. Further, systemic toxicity including adrenal suppression can occur following local corticosteroid therapy, more so in infants; and hence, potent preparations like betamethasone valerate (Betnovate), triamcinolone acetonide, fluocinole acetonide and clobetasol propionate (Dermovate) should not be prescribed for treating infantile eczema. Similarly such potent steroids should not be applied to facial skin as atrophy and telangiectasia occur more quickly on the face.

The current practice of adding a glucocorticoid to antibiotics and antifungal agents is difficult to justify. The same is true of use of glucocorticoids in ointments for hemorrhoids.

(6) *Intra-articular and intratendinous use*: Long acting esters of glucocorticoids have been used successfully to treat osteoarthritis and painful fascial tender nodules by local infiltration. Such therapy has the added advantage of minimum systemic absorption and consequent reduction in toxicity.

(7) *Diagnostic tests*: Dexamethasone suppression of adrenal function; cortisone test in hypercalcemia; prednisolone test to distinguish intra and extra-hepatic obstructive jaundice and in the diagnosis of prediabetic state.

(8) *Miscellaneous*: Glucocorticoids have been used in a wide variety of other conditions. These include: Bell's palsy, acute infective polyneuritis, encephalitis, infective hepatitis, complete heart block, hypsarrhythmia and so on. Their usefulness in the therapy of these conditions is doubtful.

They are, however, considered to be useful in reducing cerebral edema which accompanies cerebral infarction, cerebral metastases and head injury. Usually dexamethasone is used in the dose of 8 mg. four times a day. Other measures used to reduce cerebral edema are: intravenous furosemide (40-60 mg), mannitol (1 g. per kg.) or urea (1 g per kg. 30% sol.); oral administration of pure glycerine (15-30 ml. thrice daily); and rectal administration of saturated magnesium sulfate solution (50-200 ml). The use of glucocorticoids in circulatory failure is discussed in Chapter 28.

Precautions during corticosteroid therapy: These apply especially to the prolonged high-dose, suppressive therapy with glucocorticoids. They are (1) Before starting the therapy, enquire about history suggestive of peptic ulceration. Since glucocorticoids mask the symptomatology, even a minor gastric symptom should be investigated at an early stage. One should watch for the anemia due to concealed gastric hemorrhage. An x-ray of the chest may be taken to rule out tuberculosis. (2) Examine the urine periodically for sugar. (3) Keep a record of weight and blood pressure. (4) Instruct the patient never to stop the therapy abruptly. (5) If the patient develops an acute infection or has to undergo surgery, increase the dose of the steroid. (6) Glucocorticoids must not be used in the presence of infection unless the latter can be simultaneously treated with an effective antibiotic.

Contraindications: There are no absolute contraindications to glucocorticoid therapy other than Cushing's syndrome. Proper precautions have to be taken in using them in diabetes mellitus, peptic ulcer, hypertension, in debilitated or old patients and in the presence of infection.

Choice of therapy: In general, there is no difference between the therapeutic efficacy of ACTH and glucocorticoids. It has, however, been claimed that ACTH gives better results in status asthmaticus and ulcerative colitis. ACTH is preferred by many workers for treating children for prolonged periods because it is less likely to interfere with growth than glucocorticoids. ACTH is ineffective in the presence of damaged adrenal cortex. The need for injecting ACTH and its cost, however, seriously mitigate against the routine use in practice.

For routine use, prednisolone is the drug of choice as it is effective orally and cheap.

MINERALOCORTICOIDS: The important natural mineralocorticoids are aldosterone and desoxycorticosterone. They have identical effects on electrolyte and water metabolism and on cardiovascular system except that aldosterone is thirty times more potent than desoxycorticosterone.

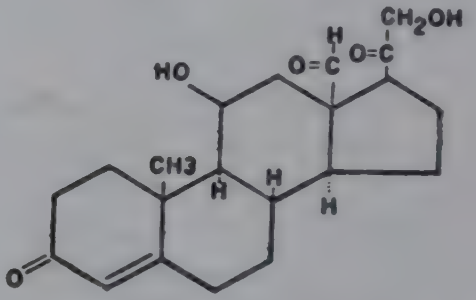


Fig. 60.6: Aldosterone.

Physiological and pharmacological actions of aldosterone:

(1) *Electrolyte and water metabolism*: In minute amounts aldosterone appears to have a 'permissive' role in allowing the kidneys to make rapid adaptations to sodium excess or deficit. It does not, however, initiate these changes itself.

Single doses of aldosterone produce sodium retention and increased urinary loss of potassium. On repeated administration of aldosterone, however, the subject escapes from the sodium retaining effect; potassium loss, however, continues. Neither aldosterone nor desoxycorticosterone has an effect on GFR and unlike hydrocortisone, neither hormone can restore the ability of excreting a water load to an adrenalectomized animal.

The results of aldosterone deficiency are clearly seen in Addison's disease. In hypopituitarism, aldosterone secretion is relatively unimpaired.

As a result of aldosterone deficiency, the renal tubules are unable to conserve sodium. There is a marked sodium loss with associated osmotic diuresis, leading to a fall in plasma sodium concentration. The extracellular fluid space becomes contracted and at the same time hypo-osmolar. As a result, water moves into the cells which become over-hydrated. Contraction of the blood volume may lead to collapse and death. Azotemia is likely to occur as a result of contracted blood volume. Potassium excretion by the kidneys is impaired. Hyperkalemia and acidosis add to the burden of metabolic disturbances. Increased intake of salt or administration of a mineralocorticoid corrects all the above abnormalities, but the muscular weakness still remains and the patient is unable to withstand stress. Addition of glucocorticoids is necessary for complete correction of circulatory instability and muscular weakness. As little as 10 μg of aldosterone injection per day can correct the above abnormalities in electrolyte and water balance.

Aldosterone exerts similar effect on cellular sodium transport at other sites.

(2) *Hypertension*: Hypertension is a characteristic feature of primary hyperaldosteronism. Hypertension due to excessive production of desoxycorticosterone is seen in one form of congenital adrenal hyperplasia. In malignant hypertension the secretion of aldosterone is found to be increased.

(3) Aldosterone is practically devoid of glucocorticoid effects.

(4) It has cardiotonic action *in vitro*.

Adverse reactions: These are related to the potent sodium retaining and potassium depleting actions and consist of weight gain, edema, hypertension and hypokalemia. Patients with Addison's disease are extremely sensitive to these effects and hence, the dose of a mineralocorticoid has to be adjusted very carefully in such patients.

Preparations and dosage:

(i) Desoxycorticosterone acetate injection I.P. is available in the concentration of 5 mg. per ml. Dose: 2 to 5 mg. daily by intramuscular injection.

(ii) Desoxycorticosterone trimethylacetate is a long acting preparation, administered intramuscularly in the dose of 25 to 100 mg. once a month.

(iii) 9*a*—fluoro-hydrocortisone (Fludrocortisone) is available as 0.1 mg. tablets. Dose: in adults with acute adrenocortical insufficiency, 1 to 2 mg. followed by 0.1 to 0.2 mg. daily as maintenance. In children upto 12 years, 0.01 to 0.05 mg. twice daily.

(iv) Aldosterone, though extremely potent, is rarely used because of its short duration of action. It may be given in the dose of 0.1 to 0.2 mg. daily orally or intramuscularly. The intravenous dose is 0.5 mg.

Therapeutic uses: The only therapeutic use of mineralocorticoids is in the management of Addison's disease.

Hyperaldosteronism: Aldosterone output may be raised in two entirely different groups of conditions:

(1) *Primary hyperaldosteronism*: This is generally due to an adenoma of the adrenal cortex. The patient suffers from hypertension, hypokalemia, polyuria, alkalosis, periodic paralysis and occasionally abnormal glucose tolerance. Edema is very rarely seen in this condition. Serum sodium and total body sodium are within normal limits as the kidneys escape from the sodium retaining effects of aldosterone after first few days. The treatment is essentially surgical.

(2) *Secondary hyperaldosteronism*: This condition occurs in edematous patients with cirrhosis of the liver, nephrotic syndrome and occasionally in congestive cardiac failure. It is especially liable to occur after sodium depletion in response to vigorous diuretic therapy Spironolactone is used to treat the resistant edema in these patients; it is discussed in Chapter 34.

MANAGEMENT OF ADRENOCORTICAL INSUFFICIENCY

Chronic adrenal insufficiency due to Addison's disease is treated by administering replacement doses of a glucocorticoid in the first instance. They are given in a dose that reduces hyperpigmentation and abolishes postural hypotension which is the hallmark of adrenocortical insufficiency. For this purpose, cortisone or hydrocortisone with its moderate salt retaining property is preferred. Cortisone may be given in the dose of 37.5 mg. daily, divided into two doses, 25 mg. in the morning and 12.5 mg. in the evening. Once the patient is regulated on cortisone or hydrocortisone, addition of 9-alpha-flurohydrocortisone (0.1 to 0.2 mg. daily), or desoxycorticosterone acetate in oil (2-5 mg. once daily) or desoxycorticosterone trimethylacetate (25 to 50 mg. I.M. once in 3-4 weeks) helps to complete the corticoid replacement therapy. If these mineralocorticoids are not available, the same purpose may be achieved by prescribing additional intake of salt (2-4 g. per day). Additional quantities of salt must not be prescribed to patients taking mineralocorticoids.

It is essential to explain to the patient that treatment of this condition is lifelong and that it is dangerous to stop it abruptly. In times of stress, the dose of the glucocorticoid must be rapidly increased 3 to 4 fold.

Acute adrenal insufficiency may arise (a) as a result of an acute infection, injury or surgery in a previously known Addisonian patient; (b) as a result of abrupt withdrawal of glucocorticoids from a patient who is on large doses; or (c) in a fulminating meningococcal infection. It is a medical emergency requiring energetic and immediate treatment. The principles of therapy are:

(a) Administration of large doses of hydrocortisone hemisuccinate intravenously (100 mg. every 4-6 hours). As such large doses of hydrocortisone cause sufficient salt retention, mineralocorticoids are not needed at this stage.

(b) Administration of adequate quantities of normal saline and glucose intravenously.

(c) Vasopressor drugs to counter the fall in blood pressure and antibiotics for infections.

Following the recovery, from third day onwards, hydrocortisone is given orally in the dose of 10 mg. four times daily. Along with it administration of a small dose of desoxycorticosterone is recommended. From the 4th or 5th day the patient is placed on the regime suggested for chronic adrenal insufficiency.

ADRENAL FUNCTION TESTS

(a) The most direct adrenal function test is the secretory rate of individual corticosteroid. These measurements are technically formidable and hence one has to rely on less direct tests as outlined below.

(b) Estimation of 17-ketosteroids and 17-ketogenic steroids gives an indirect idea about the rates of secretion of androgens (adrenal + testicular or ovarian) and hydrocortisone, respectively.

(c) *Adrenal stimulation test*: Inability of ACTH to increase the urinary excretion of 17-ketosteroids and 17-ketogenic steroids indicates absence of functioning adrenal cortical tissue and is diagnostic of Addison's disease. In Cushing's syndrome, ACTH increases the 17-ketogenic steroid excretion still further in patients with bilateral adrenal hyperplasia but not in those with adenoma or carcinoma.

(d) *Adrenal suppression test*: Exogenously administered corticosteroid suppresses release of ACTH and hence, reduces the urinary excretion of 17-ketosteroids and 17-ketogenic steroids in normal individuals and in patients with bilateral adrenal hyperplasia (with either Cushing's or Adrenogenital syndrome) but not in those with adrenal neoplasms. This is so because the hyperplasia is secondary to excess ACTH secretion whereas neoplasms are autonomous in function. Dexamethasone is generally used for this purpose.

(e) *Metopirone test*: **Metopirone** (SU 4885) is a specific inhibitor of 11-hydroxylase, an enzyme which converts desoxycortisol to hydrocortisone in the adrenal cortex. Such inhibition results in a fall in the plasma hydrocortisone level with consequent increase in ACTH output. This steps up the steroidal synthesis in the adrenal cortex. As the final step in hydrocortisone synthesis is blocked, the precursors accumulate and are excreted in urine as 17-ketogenic steroids. A paradoxical situation is thus produced by metopirone where the urinary 17-ketogenic steroid excretion increases in spite of inhibition of synthesis of hydrocortisone. This test is used mainly to guage the functional integrity of the hypothalamo-hypophyseal axis and its ability to increase ACTH output in response to reduced plasma hydrocortisone levels. This ability is impaired in pituitary disease and following administration of corticosteroids.

Metopirone is now also used in the treatment of Cushings syndrome in the same way as carbimazole is used in the treatment of hyperthyroidism. The dose ranges from 250 mg twice a day to 1 g six hourly.

61 Gonadotropins, Estrogens and Progestins

In 1911, in his studies on hypophysectomised dogs, Harvey Cushing established the role of the pituitary in regulating the gonadal function. The first substance with gonadotropic activity was isolated from the urine of pregnant women by Zondek and independently by Fluhmann in 1929.

The present evidence suggests that the anterior pituitary secretes three distinct gonadotropic hormones which can be separated chemically and immunologically. These are:

(1) Follicle stimulating hormone or FSH

(2) Luteinizing hormone or LH. It is also called interstitial cell stimulating hormone (ICSH) and

(3) Prolactin (PRL) or luteotropin.

The molecular weights of human FSH and LH are estimated to be about 32,000. However, it appears that these hormones can exist in monomer, dimer or tetramer forms. Secretion of FSH, LH and PRL is regulated by various hypothalamic releasing or inhibitory factors.

Physiology of pituitary gonadotropins: Complex interactions between the hypothalamus, the anterior pituitary and the gonadal sex steroids regulate the ovulation in women and spermatogenesis in men. This system is controlled by three feed-back mechanisms:

(1) *Long feed-back mechanism*: Gonadal sex hormones act on the hypothalamus by way of negative feed-back mechanism (estrogen, progesterone, testosterone) or a positive feed-back mechanism (estrogen, progesterone).

(2) *Short feed-back mechanism*: This involves a direct action of the three sex hormones on the anterior pituitary, regulating the secretion of the FSH and LH, and

(3) *Ultra-short negative feed-back mechanism*: This comprises regulation of the hypothalamic gonadotropin releasing hormone (GnRH) by the pituitary FSH and LH.

It appears that dopamine found at the hypothalamic nerve endings is involved in the release of GnRH, which in turn affects both FSH- and LH-secretory cells of the anterior pituitary. These secretory activities are modulated differently by estrogen, progesterone and testosterone. The mode of action of GnRH is believed to be similar in both men and women except for its cyclicity in women. It is now accepted that the hypothalamus is responsible for this cyclicity.

The regulatory mechanisms in the hypothalamus reside in two centres: (a) the 'tonic' centre in the ventromedial nucleus and the arcuate nucleus and (b) the 'cyclic' centre in the pre-optic suprachiasmatic area. In males, the tonic centre is dominant and causes activation of the pituitary and thereby a stimulation of the testes, producing normal spermatogenesis and testosterone synthesis. In females, it is probably the lack of the androgenic influence which allows the development of the 'hypothalamic clock', essential for the cyclic release of the gonadotropins. Thus, the cyclic centre is dominant in the female. This centre is sensitive to external and internal stimuli. In the presence of female sex hormones, it is activated (or suppressed) and indirectly activates the tonic centre producing an increased release mostly of LH from the anterior pituitary and consequently ovulation. The natural

GnRH isolated from the porcine, ovine and bovine hypothalami is a decapeptide. The exact structure of this hormone in the humans is not known but it is believed that the functional parts of the porcine and human GnRH are identical. Since it predominantly causes release of LH and less of FSH it is known as LH-RH. The evidence for the existence of a separate FSH-RH as distinct from the LH-RH is still insufficient.

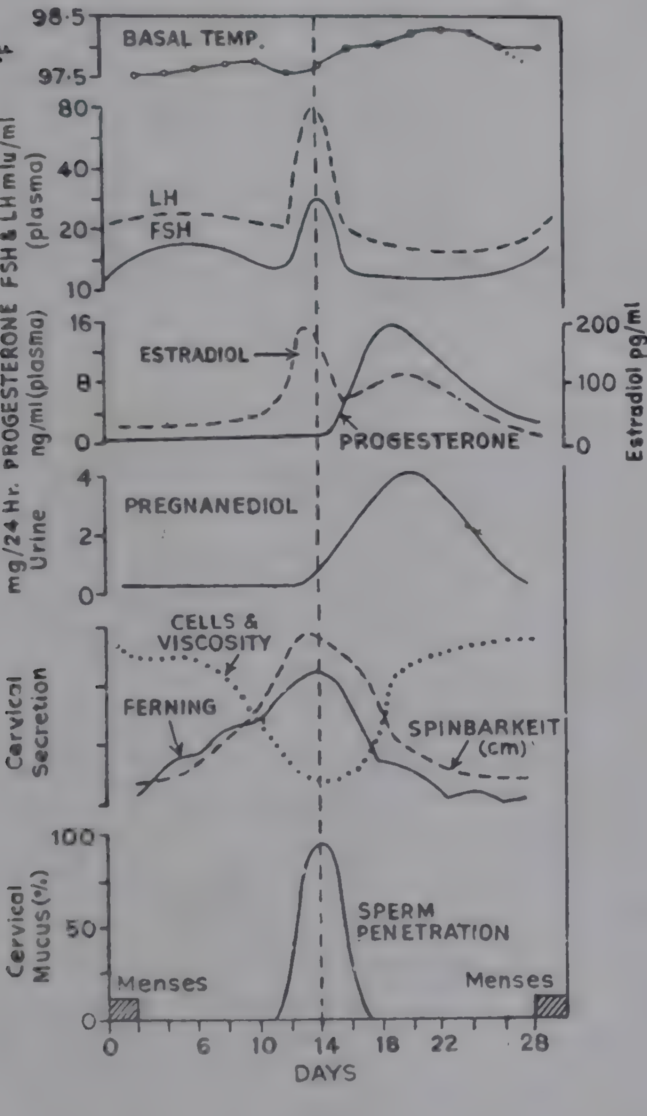


Fig. 61.1: Hormonal changes in blood and urine during the menstrual cycle in a human female.

The sequence of various hormonal changes that seem to occur during a normal 28 days menstrual cycle in woman is shown in figure 61.1. Day one is defined as the first day of menstrual flow, while the day preceding the first day of the next menstrual flow is designated as the last day of the cycle. Generally, cycles between 21 and 35 days are accepted as normal, the duration of menstrual flow being 2-7 days.

Ovarian follicular growth, once initiated by FSH, proceeds independently to the preovulatory phase. A rise of FSH early in the cycle is followed by a rise in blood estradiol. Under the influence of FSH alone, the follicle cells do not secrete estrogens unless a small amount of LH is also present. Such FSH stimulated follicles undergo atresia unless a large quantity of LH is secreted. The ovulatory peaks of FSH and LH occur between days 11-23 of the menstrual cycle when the estrogen concentration is falling to basal levels (Fig. 61.1.). Its timing has no relationship to the length of the cycle. Following this large quantity of LH (and ?FSH), the follicle size increases considerably resulting in follicular rupture and release of an ovum. Recent studies indicate that peaks of plasma estradiol and 17-alpha hydroxyprogesterone precede the mid-cycle LH peak. This indicates that theca interna cells which predominantly synthesise estradiol produce 17-alpha hydroxy progesterone as an intermediate product. Estimation of these hormones, therefore, gives some idea regarding the follicular function. Following rupture, the follicle undergoes reorganization to form a corpus luteum, which secretes mainly progesterone, 17-alpha hydroxyprogesterone, estradiol and some other steroids independently of LH-FSH control.

Corpus luteum is an independent endocrine organ. In rodents, corpus luteum has limited life span of 3-4 days unless prolactin is secreted by the pituitary. Hence, in this species, prolactin acts as luteotropic hormone (LTH) necessary for initiation and maintenance of corpus luteum. Such luteotropic role of prolactin (LTH), however, has not been demonstrated in human females in whom LH itself is considered to be luteotropic. The life span of corpus luteum during a non-pregnant cycle in humans averages about 11 days, while the functional life span of the corpus luteum of pregnancy is 9-10 weeks. Since 17-alpha hydroxyprogesterone is synthesized mainly by the corpus luteum (and not by human placenta) its blood level reflects the function of corpus luteum during pregnancy.

The present data indicate that the preovulatory LH surge is, apparently, partly initiated by an increase in the pituitary sensitivity to GnRH. This increase in sensitivity is the result of the high estradiol levels present at this time of the cycle. In addition, an increased discharge of GnRH has been demonstrated at this stage. Thus, in response to the 'ovarian signal' (in the form of estradiol) a large quantity of LH is released abruptly, leading to ovulation and the subsequent formation of corpus luteum. The large quantities of estrogen and progesterone found after ovulation apparently suppress the sensitivity of the hypophysis to GnRH, in addition to suppressing the hypothalamus. Following this, urinary level of estrogen falls while the urinary pregnanediol level starts rising, indicating increased secretion of progesterone (Fig. 61.1). Thus, the urinary pregnanediol which is insignificant before ovulation reaches the level of 4-10 mg. per 24 hours during the secretory phase. Unlike that of most other mammals, the human corpus luteum secretes estradiol as well as progesterone. In the absence of conception, the progesterone and estrogen levels remain high for eight days and then fall abruptly leading to menstruation. These hormonal changes before and after ovulation are associated with the characteristic endometrial changes of 'proliferative phase' and 'secretory phase' respectively.

Although it is difficult to predict the day of ovulation in a given cycle in a human female, the reproductive cycle shows a remarkable regularity and in the majority, it is repeated every 26-30 days. What keeps the system cycling so regularly is not well understood. The usual way of judging ovulation clinically by noting the rise in basal body temperature (BBT) is not accurate, since this rise, occurring as a result of the thermogenic activity of progesterone, takes upto five days to reach or exceed 98°F.

Gonadotropic hormones stimulate hormone biosynthesis in the gonads. The exact mechanism of their action is not known. However, it has been observed that LH increases the accumulation of adenosine 3', 5'-mono-phosphate (cyclic AMP) as one of its early effects. At the cellular level cyclic AMP triggers off the reaction of synthesis of various sex hormones starting from C_{27} compound cholesterol. During the synthesis, at various stages, carbon atoms are removed or replaced resulting in formation of various C_{21}, C_{19} and C_{18} sex steroids (Fig. 61.2). As seen in this figure, androgens are obligatory precursors of estrogens and progesterone is necessary for the synthesis of androgens.

The principle estrogens produced in ovaries are 17-beta estradiol and estrone and very little estriol. It should be noted, however, that these three compounds together account for only 40% of the biological activity extracted from the follicular tissue. It is believed that major secretion of ovary is estradiol and that it is peripherally converted to estrone and estriol.

Apart from estrogens and progesterone, the ovarian extract also contains 17-alpha-hydroxyprogesterone and androstenedione, a precursor of testosterone.

Hypothalamo-pituitary-ovarian relationship: It is now accepted that the secretion of LH and FSH from the anterior pituitary is regulated by the interaction between the sex steroids and hypothalamic gonadotropin releasing hormone(s). Both progesterone and testosterone suppress the discharge of LH and FSH stimulated by LH-RH. In contrast, estrogen appears to exert a biphasic effect on the pituitary response to hypothalamic LH-RH in rats. In small doses it causes early inhibition of the response to LH-RH, followed later by an enhancement of this response with the consequent release of LH and FSH. In humans, this biphasic effect appears to be dose dependent as well as time dependent.

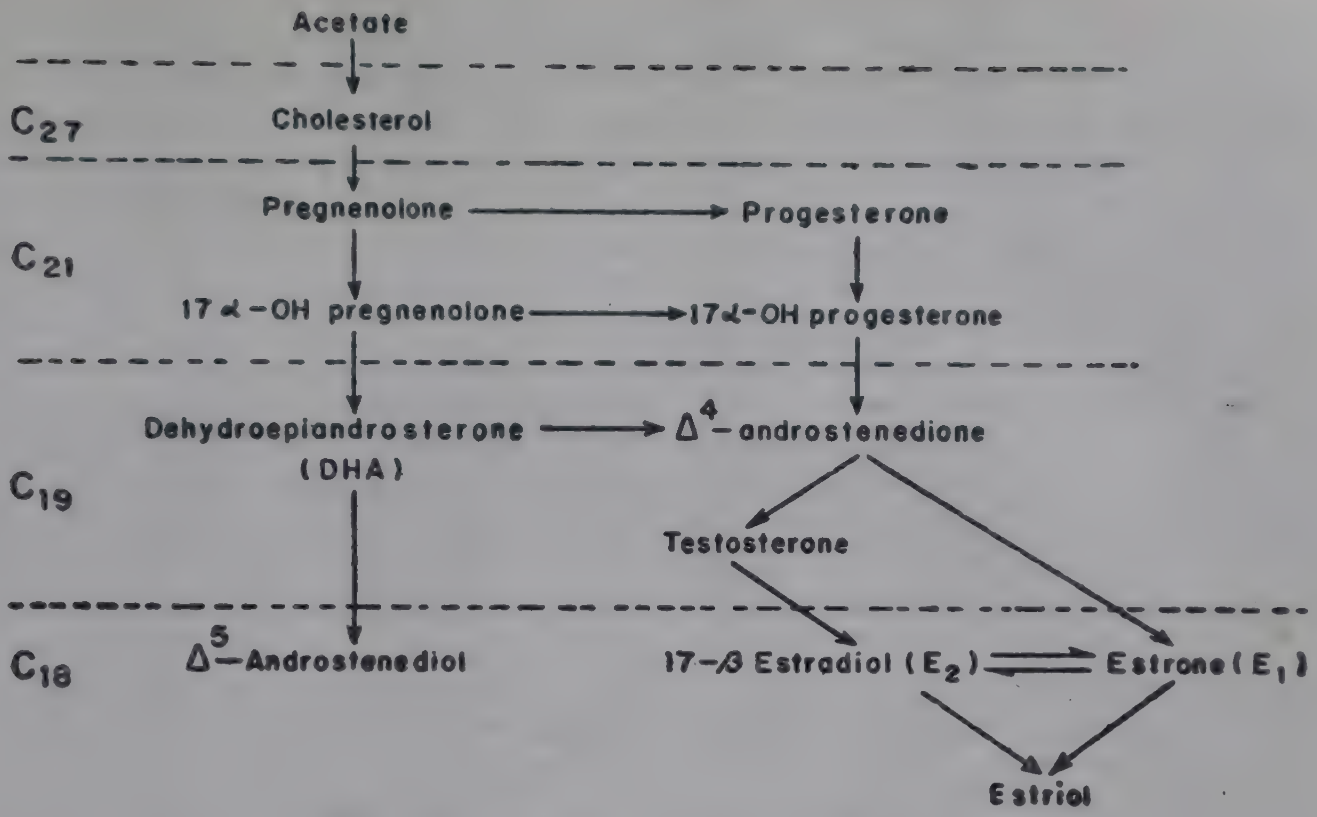


Fig. 61.2: Biosynthesis of sex-steroids in the gonads.

Larger doses of estrogen inhibit the response to LH-RH and decrease the release of FSH and LH. However, it is known that continuous administration of estrogen can suppress the synthesis and release of FSH and LH, and the increased levels of urinary gonadotropins observed following the menopause are mainly due to the removal of estrogen inhibitory influence.

LH-RH: The LH-releasing factors of ovine and porcine origin have been isolated, identified and now synthesized. They are identical in structure. The synthetic LH-RH is a decapeptide pGlu-His-Trp-Ser-Tyr-Gly-Leu-Arg-Pro-Gly-NH_2. This compound is highly active in many animal species including the humans. Administered subcutaneously, intramuscularly and intravenously, it causes marked increase in plasma LH and to a smaller extent in plasma FSH levels. It also stimulates the synthesis of LH in the pituitary. Further, it can induce ovulation in animals. Interestingly, LH-RH stimulates the secretion of LH and FSH even in animals that have been pretreated with very large doses of progesterone, estradiol or testosterone. It thus differs from TRH since administration of thyroxine inhibits the TSH secretion normally induced by TRH.

Clinically, LH-RH has been used to elucidate the differential diagnosis of both primary and secondary amenorrhoea in women and hypogonadism in men. However, the results of such testing are not always conclusive. Therapeutically, it has been used to induce follicular growth, maturation and ovulation in women and to restore libido, potency and spermatogenesis in males with hypogonadotrophic hypogonadism. These studies are still in the experimental stage. The major drawback of LH-RH is its very short half life of about 2 minutes. Hence, superactive analogues with longer biological activity are now being investigated. Further, the possibility of using inhibitory, antagonistic analogues as contraceptives is also being studied.

GONADOTROPINS

The gonadotropins now available for human therapy are:

(1) Human chorionic gonadotropin (HCG).

(2) Human pituitary gonadotropin (HPG), and

(3) Human menopausal urinary gonadotropin (HMG).

All the gonadotropins are polypeptides and are destroyed by the enzymes, when given orally. They are effective only when given by injection. The metabolism of these hormones varies considerably. Injected HCG remains in the blood for longer time and is excreted slowly in the urine. Others are degraded in the body before excretion.

All gonadotropins are capable of eliciting antibody formation in heterologous species. Antihormones thus formed are specific for the particular antigen employed.

Bioassay: These are usually conducted on hypophysectomised immature rats and mice and are based on the measurement of increase in ovarian or uterine weight (for FSH), increase in weight of the ventral prostate (for LH), or histological changes in the ovary, uterus and vagina. For routine tests of pregnancy, simple procedures are used to detect the chorionic gonadotropin in the urine. These tests are based on observation of ovulation in the rabbit (Friedman test), or in the mouse (Ascheim Zondek test), or ovarian hyperemia in immature rats or presence of spermatozoa in the cloaca of the male frog (Frog test), a few hours after the injection of the urine sample in these animals. Radioimmunoassay procedures are now available for estimating the plasma levels of FSH, LH and HCG.

HUMAN CHORIONIC GONADOTROPIN (HCG): It is a hormone of human pregnancy and is secreted by the foetal placenta. It can be detected in the plasma by RIA, several days before the first missed period. Sufficient amount of it can get absorbed into the blood and sustain luteal function until the placenta starts secreting estrogen and progesterone by the 3rd month of pregnancy.

Pharmacological actions: Chemically, the amino acid sequence of HCG-beta unit resembles that of human LH-(beta) unit and HCG has some similarity of action to pituitary LH. Thus, small doses can preserve the corpus luteum and prolong the secretory phase of the menstrual cycle in human female. This is associated with an increased urinary excretion of pregnanediol. The hormone is capable of inducing a decidual reaction in the endometrium even in the absence of conception (pseudopregnancy). It does not promote follicle maturation in humans and its ability to induce ovulation by itself is doubtful. However, administered to immature animals, it can evoke follicular growth and induce ovulation.

Injected into the males, HCG stimulates the interstitial cells of the testes to secrete androgen.

Preparation and dosage: HCG (Antuitrin-S, APL, Pregnyl) is available as powder 5,000 I.U., 10,000 I.U. and 20,000 I.U. with 10 ml container of diluent.

Therapeutic uses:

(1) **Infertility:** HCG therapy is capable of inducing ovulation in an adequately developed follicle following endogenous or exogenous FSH (HPG or HMG), leading to conception. This is discussed below in detail.

(2) **Cryptorchism:** Failure of the testes to descend is not an uncommon finding in childhood. In majority of the cases, the descent occurs at the time of puberty. Cryptorchism denotes failure of the testes to descend into the scrotum, even at puberty. HCG is used to promote this descent. It is given in doses of 1000 to 4000 I.U. twice weekly for several weeks. The hormone should not be used if mechanical obstruction prevents the normal descent.

(3) **Delayed puberty** in boys can be treated with HCG. Similarly, when the distinction between primary testicular failure and gonadotropin failure is not clear and laboratory tests are not available for this purpose, a therapeutic trial with HCG is justified. Thus, the puberty is induced and often maintained without further treat-

ment after a course of HCG.

(4) **In the diagnosis of Stein-Levinthal syndrome,** gonadotropin stimulation test of the ovarian function is often helpful.

HUMAN PITUITARY GONADOTROPIN (HPG): This has been prepared from human pituitary glands. It is a crude preparation and has a strong FSH-like and a little LH-like activity. It can stimulate follicular growth and estrogen production in amenorrheic women. HPG is mainly indicated in patients with low urinary gonadotropins and low urinary estrogens. In such cases, if it is followed by HCG (5000—10,000 I.U.), the combination can produce luteinization and ovulation which can lead to successful conception. It is not expected to be effective in cases with primary ovarian failure with increased urinary gonadotropins.

The hormone is biologically standardized with reference to international reference factor (IRF) and is administered in IRF units. Usually 1 mg. active preparation can be obtained from about 10 human pituitaries and contains 500-750 I.U.

HPG in combination with HCG is used in the treatment of infertility. A universally acceptable dose regime for this combination is not yet established. Usually, it is necessary to individualize the dose of HPG. Initially, subovulatory doses should be given in order to select the dose since the variation in dose requirement is very wide. Increasing doses are then tried in subsequent cycles. Repeated monitoring of urinary estrogen excretion can indicate the state of follicular maturation.

Adverse effects of HPG-HCG combination: The incidence of multiple births is very high with a high rate of miscarriage as it causes multiple ovulation. Live births have been reported of sextuplets while abortions of 5-9 have been noted. Obviously, prematurity increases the risk of foetal mortality and foetal wastage.

The combination sometimes causes the '*hyperstimulation syndrome*' with serious risk to life. It is due to excessive stimulation of ovaries, leading to ovarian enlargement and multiple cyst formation, hemoconcentration and a tendency to thrombosis. Huge ovaries occupying almost the whole abdomen have been reported. Ovaries become friable and can rupture during abdominal palpation or coitus. Thus, internal hemorrhage due to bleeding from the ruptured follicle can be a fatal complication. Mild cases may have abdominal pain, nausea, distension and ascites. Various dose schedules are now being investigated to find out if these adverse effects can be minimized without affecting the therapeutic usefulness of the combination.

HUMAN MENOPAUSAL URINARY GONADOTROPIN (HMG, Menotropins): The presence of gonadotropic substances in the menopausal urine was noted by Fluhmann and Zondek over thirty years ago. However, HMG has been reasonably purified and used clinically only recently. HMG when injected, has actions similar to HPG and when used in combination with HCG can induce ovulation in women with amenorrhea. It has similar disadvantages as HPG. It is non-antigenic in humans.

The commercially available preparation 'Pergonal' is a standardized potent product containing both FSH and LH activity in 1:1 proportion. It acts predominantly like FSH and has similar applications as HPG. It is given intramuscularly in the dose of 75 I.U. of FSH (and also 75 I.U. of LH) daily for 9-12 days, followed by 10000 I.U. of HCG one day after the last injection of menotropins.

PROLACTIN: Although this pituitary hormone was demonstrated in animals, its presence as a separate entity in humans was doubted until recently. Ample evidence now indicates that the human pituitary gland secretes prolactin (hPRL, M.W. 17,300) which has some similarities to that of PRL obtained from the sheep pituitary gland. Serum prolactin can now be measured by very sensitive tissue binding or radioimmunoassay methods. The prolactin producing cell has been identified in human and monkey pituitary glands.

Unlike with the other pituitary hormones, the secretion of prolactin is inhibited by a hypothalamic prolactin-inhibiting factor (PIF). There is also some evidence (though not a conclusive one) for a prolactin-releasing factor (PRF). PIF is synthesized probably in the same region of the hypothalamus as LH releasing factor (LHRF), which can explain the common association of galactorrhea and amenorrhea. The present evidence indicates that the release of PIF is under dopaminergic control; the hypothalamic receptors involved are highly specific for dopamine. Thus, the administration of 1-dopa may cause an increase in PIF secretion resulting in inhibition of hPRL secretion.

Prolactin secretion is increased following the drugs which deplete dopamine such as reserpine and methyldopa or which block dopamine receptors such as metoclopramide and phenothiazines like chlorpromazine. They are also known to affect other hypothalamic biogenic amines. It is suggested, therefore, that hypothalamic regulation of hPRL secretion is mediated by a balance between inhibitory dopaminergic and stimulatory 5-hydroxytryptaminergic mechanisms. Prolactin is also released following the administration of thyrotrophin releasing factor (TRF).

Prolactin is luteotropic only in certain species like the rat and the mouse. In man, LH itself serves the luteotropic function. The main action of prolactin is probably the initiation and maintenance of lactation. The hormonal mechanism that converts the developed and potentially secretory mammary gland into an active secretory organ at delivery is complicated and not well understood; but other hormones such as estrogens, corticosteroids, insulin and thyroid are also necessary for efficient galactopoiesis. Serum hPRL concentration increases progressively during pregnancy and postpartum. Breast feeding and stimulation of the nipple can cause a marked rise in serum hPRL levels. Increased hPRL levels are also observed following exercise, psychological and surgical stress and high doses of estrogens. The significance of this is not known but the possibility of prolactin having general metabolic actions cannot be ruled out. The hormone has been shown to cause changes in the cardiac rhythm and rate.

Experimental work in mice and rats has indicated the possible involvement of prolactin in the genesis of mammary cancer. Various clinical syndromes associated with galactorrhea, amenorrhea and hyperprolactinemia have been described in humans. The rational therapy of these would be to use the drugs that decrease the hPRL secretion. The two drugs presently employed are 1-dopa (see Chapter 19) and bromergocryptine.

BROMERGOCRYPTINE (Bromocriptine, Parlodel): 2 Bromo-α-ergocryptine, a semisynthetic ergot alkaloid is a dopaminergic receptor stimulant. It inhibits lactation and other prolactin dependent phenomena in experimental animals by suppressing the prolactin secretion. The drug acts directly on the prolactin secreting cells of the pituitary as well as on the hypothalamus. It has negligible oxytocic and cardiovascular actions. Bromocriptine has been administered to patient with galactorrhea-amenorrhea-hyperprolactinemia syndrome. In such cases it produces a fall in the serum hPRL accompanied by cessation of milk secretion and restoration of the normal cyclic ovarian activity. The drug may inhibit tumour growth in pituitary prolactinomas. It is, however, not effective in amenorrhoea due to gonadotropin deficiency or ovarian failure. Bromocriptine can also suppress puerperal lactation.

It is given orally in the dose of 2.5 mg 2-3 times daily, during meals. Menstruation usually returns within four weeks but occasionally the response takes several months. Large doses of bromocriptine produce a fall in GH levels in patients with acromegaly and its role in the management of acromegaly remains to be defined. Similarly, large doses have also been used to treat parkinsonism (see Chapt. 19). Bromocriptine in the dose of 1.25 mg once daily at dinner time, increased every third day upto a maximum of 15 mg, has been reported to be useful in chronic porta-systemic encephalopathy. The successful use of this drug and of levodopa in hepatic encephalopathy supports the view that at least a part of the symptomatology is due to a defect in dopaminergic neurotransmission. The drug is prohibitively expensive at present.

Adverse reactions: These include gastric upset, nausea and drowsiness. Continuous high doses may cause constipation, nasal congestion, cramps in legs, hallucinations, dystonic reactions, arrhythmias and postural hypotension.

PLACENTAL HORMONES

The placenta develops during pregnancy and serves the important function of sustaining the growth and nutrition of the developing embryo. In addition to this, it is an endocrine organ secreting various hormones. One of these, the chorionic gonadotropin (HCG), is already discussed. HCG appears in the urine very early after implantation of the fertilized ovum and disappears from the urine within a few days after delivery. Factors that control the production of HCG are not known. It helps to maintain the functioning corpus luteum during early pregnancy.

Recently, another placental peptide related to human pituitary growth hormone has been isolated. The substance probably has lactogenic, luteotropic and growth promoting activities. It is present in human serum, urine and amniotic fluid during pregnancy and disappears immediately after delivery. The hormone is named '*placental growth hormone* or *placental lactogen*'. Its role in human pregnancy is still under investigation, but it is believed to act as a metabolic hormone in the mother and the placenta. A thyroid stimulating principle, different from the pituitary TSH, has also been isolated from the placenta.

During pregnancy (probably from the 3rd month), the placenta produces large amounts of estrogen and progesterone. The placental progesterone, besides having a physiological effect on maternal organs, also acts as an important precursor for foetal corticosteroids and androgens. It is now known that the urinary estrogen levels provide a more sensitive index of foetal well-being than the urinary pregnanediol levels. This is because estriol excretion is directly dependent on foetal metabolism. During pregnancy, the urinary excretion of estrogen shows a great preponderance of estriol over that of estrone and estradiol. Since the fetus is known to play a specific role in the synthesis of estriol, assay of the level of estriol in maternal urine provides useful information about the well-being of the foetus. A fall in urinary estriol level may denote foetal distress or retarded foetal growth.

Although the placenta contains large amounts of corticosteroids there is no conclusive evidence to suggest that these are synthesized in the placenta.

ESTROGENS

In humans, the estrogens are produced mainly by the ovary and the placenta; small amounts may be produced by the adrenals and testes. The synthesis of estrogens from acetate and cholesterol is shown in Fig. 61.2. In certain animals like the horse, large quantities of estrogens are produced by the testes. Estrogens are also present in various plants and seeds. The natural estrogens are steroids. However, typical estrogenic activity is also shown by chemicals which are not steroids. Hence, the term 'estrogen' is used as a generic term to describe all the compounds having an estrogenic activity.

The role of the pituitary gondatropins in regulating the estrogen-progesterone production has been discussed. During childhood, small amounts of these pituitary hormones keep up a limited output of estrogenic and androgenic hormones which bring about the normal, gradual development of the genitalia. At the time of puberty, the output of gonadotropins increases with corresponding activation of the gonads, leading to an increased production of the ovarian estrogens. The stimulus that brings about such a spurt in activity at puberty is not known. Changes occurring in the rate of estrogen secretion during the reproductive cycle have been described previously.

Physiological functions of estrogens: These are,

(1) The development of the reproductive tract in the female e.g. uterus, fallopian tubes and vagina.

(2) The development of female secondary sex characters, such as breast (ductal growth), body contour, hair, skin and voice. They are also responsible for the psychological and emotional get up, typical of feminity.

(3) Stimulation of the proliferative or preovulatory phase of the endometrium. The cyclical changes in estrogen secretion during the normal menstrual cycle and inhibitory role of excessive estrogens on pituitary FSH have already been discussed.

(4) Vasodilatation of capillaries in general and those of the endometrium in particular.

(5) Metabolic effects such as retention of nitrogen, sodium and fluid in tissues; maintaining blood cholesterol level lower than that observed in males.

(6) Promotion of the union of the epiphyses with the metaphyses, thus controlling the stature and height in females. Because of this action, the epiphyseal fusion is accelerated following the onset of menarche in females and once the epiphyses are fused, no further increase in height can occur.

Classification of estrogens: These drugs can be classified into three groups:

I. *Natural estrogens* e.g. estradiol, estrone and estriol.

II. *Semisynthetic estrogens* e.g. ethinylestradiol.

III. *Synthetic estrogens*: Those which are steroids e.g. mestranol and those which are not steroids but derivatives of diphenyl-ethylene (stilbene) e.g. stilbesterol (Fig. 62.1) or triphenyl-ethylene e.g. chlorotrianisene (TACE).

All the estrogenic compounds produce similar pharmacological actions and hence, are discussed together.

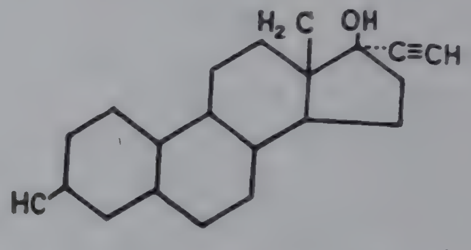


Fig. 61.3: Estradiol.

Pharmacological actions: These drugs, when used as substitution therapy, produce actions similar to the physiological actions of natural estrogens. The mechanism of action of estrogens is not well understood. The concept of estrogen receptors is rather complex in the light of the diverse actions of these hormones. There appear to be a finite number of such receptors in the cytoplasm and the nucleus of the target cells. Some evidence indicates that the estrogens stimulate the synthesis of prostaglandins in the target cells and that progesterone blocks their release. Their other pharmacological actions are:

(a) **Estrogen and menstruation:** In the absence of adequate ovarian function, estrogens administered in appropriate doses produce proliferative changes in the myometrium and the endometrium. Following these changes, withdrawal of estrogens causes menstrual flow known as 'withdrawal bleeding'. This obviously cannot be compared with the natural menstruation where progesterone withdrawal plays an important role. The response depends upon the size of the dose and the duration of treatment. With very small doses irregular bleeding can occur even without the interruption of the drug.

(b) **Gonadotropin inhibition:** Continuous administration of estrogens suppresses the secretion of FSH and also of midcycle LH surge resulting in inhibition of ovulation. In males, it inhibits spermatogenesis. The testes may undergo atrophic changes and the secretion of androgen is reduced.

Administration of estrogens, however, even in large doses, after the ovulation, does not affect the course of normal menstrual cycle.

Estrogens can also suppress lactation by inhibiting gonadotropins.

(c) **Metabolic actions:** Given over a long period these drugs may occasionally cause sodium and water retention. Estrogens also reduce the level of circulating lipids, including blood cholesterol. They have a weak anabolic action.

Large doses of estrogens given over a long period can inhibit the growth of epiphyseal cartilage.

(d) **Carcinogenicity:** Estrogens have been shown to be carcinogenic in animals like mice.

(e) **Antiandrogenic action:** Topical application of small amount of estrogen can counter the action of the androgen on capon's comb. Estrogens have been found to be beneficial in prostatic cancer which is probably androgen dependent.

Absorption, fate and excretion: Both the natural and synthetic estrogens can get absorbed through the skin and the mucous membranes and thus, can produce systemic effects. Given orally, estrogens are well absorbed but the natural estrogens are not therapeutically so effective as they are metabolised during their passage through the liver. Enterohepatic circulation of estrogen does occur.

Studies with radioactive estradiol in women indicate that about 65% of the dose is excreted in the urine, 20% of which is estradiol and the rest as metabolites. About 10% of the dose is recoverable in feces and the fate of the remaining 25% is unknown. Liver plays an important role in the conjugation of steroidal estrogens. Nonsteroids do not metabolize so easily and hence a large fraction of nonsteroidal estrogens such as diethyl-stilbestrol is excreted in urine in free state.

Natural estrogen esters like benzoate and dipropionate, when injected, are absorbed slowly and are effective for several days or weeks.

Bioassay: The crystalline pure estrogenic preparations need no bioassay. The activity of estrogenic substances is bioassayed in rats by the method of Allen and Doisy, which is based upon the observation of typical cornified vaginal smear following estrogen administration. This test is very sensitive, particularly if the agent is applied locally into the vagina of the test animal.

Adverse reactions: The most common effect is anorexia and nausea. Vomiting, dizziness and diarrhoea may sometimes occur. It may be noted that such nausea and vomiting is observed during early pregnancy and is known as morning sickness. Estrogens may also cause water retention, breast engorgement, thrombophlebitis, leg cramps and alterations in liver function. Increased incidence of gallstones has been reported in women taking oral contraceptive pills. The steroid estrogens can induce or exacerbate porphyria in susceptible individuals. Development of endometrial carcinoma after stilbestrol therapy in patients with Turner's syndrome has been reported. Further, an increased incidence of vaginal and cervical adeno carcinoma has been reported in the female offsprings of women who have taken synthetic estrogens during the first trimester of pregnancy.

It must be emphasized that pharmacological doses of estrogens administered to immature or young girls can cause premature development of secondary sex characters such as growth and proliferation of mammary gland tissue and lead to precocious puberty. Further the drug may stunt the growth of the long bones by accelerating the closure of the epiphysial plate.

Preparations and dosage:

(a) *Natural estrogen*:

(i) Estradiol, micronized, 1 mg, 2 mg

tablets for oral use. For i.m. use, it is available as injection 1 mg./ml. in 10 ml. containers.

(b) *Semisynthetic steroid estrogens*:

(i) Ethinyl estradiol available as tablets containing 0.05 mg. of the drug for oral administration. For doses see the text. In the treatment of prostatic cancer the dose recommended is 1-2 mg. daily.

(ii) Estradiol benzoate injection I.P. usually contains 1 mg. per ml. The effect lasts for several days; dose 1 to 5 mg. by intramuscular injection.

(iii) Estradiol dipropionate I.P. is administered in the same dose and by the same route as the benzoate. It is given once in 1-2 weeks.

(iv) The long acting intramuscular estrogen preparations available are estradiol cypionate, administered every 1 to 2 weeks in the dose of 1 to 5 mg., estradiol undeconate, given in the dose of 100 mg. every 3 weeks (mainly in prostatic carcinoma) and estradiol valerate (Progynon), 5 to 20 mg. of which are given at intervals of 2 to 4 weeks.

(v) Quinestrol is an orally active, very long acting estrogen used in the preparation 'the once-a-month pill' oral contraceptive. Chemically, it is 3-cyclopentyl ether of ethinyl estradiol.

(vi) Mestranol is the 3 methyl ether of ethinyl estradiol. It is more potent and is active by mouth. It is mainly used along with progestins (see Chapter 62).

(c) *Conjugated estrogen* (Premarin): This preparation, obtained from urine of pregnant mares, contains water soluble conjugated forms of the mixed estrogens. It is available as 0.625 and 1.25 mg. tablets and as an injection containing 20 mg. of the drug in 5 ml. The dose for control of excessive menstrual bleeding is 20 mg. by slow intravenous injection.

(d) *Synthetic nonsteroidal estrogens*:

(i) Diethylstilbestrol (Stilbestrol) tablet contains 0.5 mg. For doses see the text. It is given orally. It is the most potent nonsteroidal estrogen.

(ii) Diethyl stilboestrol diphosphate can be administered by intravenous injection. It is available as 250 mg. in ampoules and as 50 mg. tablets for use in prostatic carcinoma.

(iii) Diethyl stilboestrol dipropionate is administered intramuscularly. Dose: 0.5 to 5 mg. twice or thrice a week.

(iv) Dienoestrol I.P. is available as 1 mg. tablets. Dose: for menopausal symptoms, 0.5 to 5 mg. daily.

(v) Chlorotrianesene (TACE) is a synthetic nonsteroid estrogen. It is stored in the body fat and converted to its active estrogenic form, probably in the liver. It is available as 12 and 25 mg. capsules. It is rarely used.

(vi) The other preparations available for therapy include benzestrol, hexestrol, promethestrol and methallenestril.

Therapeutic uses: Parenteral estrogen preparations are now rarely used as the synthetic preparations are highly effective orally. The preparations commonly employed clinically are ethinyl estradiol, mestranol, stilboestrol and dienestrol. Ethinyl estradiol and its 3 methyl-ether (mestranol) are the two most potent drugs while stilbestrol is probably the cheapest preparation. In therapeutic potency, 1 mg. of ethinyl estradiol is equivalent to 20 mg. of stilbestrol, 80 mg. dienestrol and 400 mg. hexestrol. The important therapeutic uses are:

(1) **Amenorrhea:** Delayed menarche is many times constitutional and occasionally menstruation may not start even up to 18 years of age; the individual is otherwise normal. The usual treatment in such cases is to attend to the general health and to reassure the anxious mother. A girl who does not menstruate even by the age of 18 years usually has some pathology and needs to be investigated and treated according to the cause. It should be noted that psychogenic disturbances may have profound effect on menstrual periodicity and flow.

In amenorrhea due to pituitary failure the ideal treatment would be to use gonadotropins as discussed earlier. However, estrogens can be used to produce cyclic withdrawal bleeding in both primary and secondary amenorrhea. Usually, 0.05 mg. of ethinyl estradiol is given daily for 24 days with addition of an oral progestin during the last 8-10 days of estrogen therapy. This is followed by 'withdrawal bleeding' within 3-5 days. The therapy is restarted five days after the onset of bleeding. Such therapy may be necessary almost for a life time in patients with marked ovarian failure (e.g. Turner's syndrome) or where ovaries have been removed.

Estrogens used at the appropriate time, in patients with prepuberal ovarian failure, will bring about growth, genital development and secondary sex characters in almost normal fashion.

(2) **Menopausal syndrome:** As age advances, the ovarian function decreases resulting in menopause. The menstrual irregularity observed just prior to the menopause is due to anovulatory cycles which can be treated by cyclic administration of progestins. The occurrence of menopause is sometimes followed by such symptoms as hot flushes, fatigue, loss of concentration, muscle cramps, anxiety, insomnia, vertigo, myalgias and arthralgias. Urinary urgency or incontinence may be present, and fainting and syncope, may also occur. Mild cases need no more treatment than proper explanation of natural physiological processes, reassurance and a tranquillizer or a placebo. Those with genuine symptoms for which they demand relief may be treated with an estrogen, provided there are no contraindications. The lowest possible dose should be used to maintain the patient symptom-free. The dose may be administered cyclically for 20-25 days a month for a few cycles. The major risk of prolonged low dose estrogen treatment in post menopausal women appears to be endometrial carcinoma. Diethylstilbestrol 0.5-2 mg. or ethinyl estradiol 0.02-0.05 mg. daily for 4 weeks, followed by rest for one week, is usually recommended. Some authorities administer small doses of androgens, along with estrogens to have better anabolic effect. Estrogens also help to clear senile vaginitis and kraurosis vulvae, a condition associated with itching and infection of the vulva; in such cases dienoestrol vaginal cream may be used locally.

(3) **Vulvo-vaginitis in children:** In this condition, the infection persists because the vaginal pH at this age is alkaline, and the epithelium is columnar and these are not hostile to the growth of pathogens. Following estrogen therapy the vaginal epithelium cornifies with the deposition of glycogen. The glycogen is converted into lactic acid by the *Doderlein bacilli,* resulting into acidic pH, which prevents growth of bacteria. Ethinyl estradiol in the doses of 0.02-0.05 mg. daily for 6-7 days along with a proper antibiotic is usually recommended. The combination can also be used topically.

(4) **Functional uterine bleeding:** Usually, oral progestins are preferred in this condition. However, estrogens are useful when a rapid hemostatic effect is desired. Large doses of estrogens, 4-5 times the usual therapeutic dose, are necessary.

(5) **Osteoporosis:** This condition, seen in both sexes (commoner in females), is characterised by thinning and weakening of the bones. It is usually seen in postmenopausal women (postmenopausal osteoporosis). Estrogens produce some short term benefits, probably by slowing or arresting the progression of bone loss (bone resorption). They do not significantly increase the skeletal radiodensity even after years of treatment. The most effective treatment of this condition is believed to be the increase in daily calcium intake to 2-2.5 g. Estrogens and vitamin D in therapeutic doses may be added.

(6) **As oral contraceptives:** See Chapter 62. Diethyl stilbestrol in large doses (20 mg twice a day) may be used for 3-5 days immediately after rape in order to prevent conception.

(7) **Prostatic cancer:** The use of estrogens in this condition is discussed in Chapter 55.

(8) **Acne and hirsutism:** Estrogens are sometimes used to control excessive acne in both sexes. They probably act because of their antiandrogenic action. However, their serious adverse effects should be borne in mind before prescribing these drugs in males for such a relatively trivial condition. In women, ethinyl estradiol may be used cyclically, 0.01-0.1 mg daily, from 5th to 25th day of the menstrual cycle.

Estrogens can also be used to treat hirsutism in females, where no endocrine cause is detected. They probably act by suppressing the ovary. Usually, diethylstilbestrol in doses of 2 mg. daily is given in a cyclic fashion over a long period.

(9) **Miscellaneous uses:** Estrogens are sometimes used to suppress lactation and relieve the engorgement of the breast, which is necessary in cases with breast abscess. Stilbestrol in doses of 5 mg. thrice daily for 3 days followed by 5 mg. daily for 5 days is usually recommended.

Estrogens have been used to reduce blood cholesterol levels in patients with coronary insufficiency. Although these drugs can reduce the cholesterol level, their usefulness in reducing the mortality or preventing the attacks of myocardial infarction is highly controversial. They are also used empirically in the treatment of orchitis in mumps, with equivocal results.

PROGESTERONE AND OTHER PROGESTINS

The first effective progestational substance was isolated by Corner and Allen (1930) from the corpus luteum. They also described the 'progestational proliferation' of the endometrium and showed that corpus luteum was necessary for the preparation of the uterus for successful nidation of the fertilized ovum. The hormone, however, could not be used therapeutically because of its short action, ineffectiveness by oral route and short supply. The recent introduction of new, orally effective progestational drugs has revolutionized pharmacotherapeutics in gynecologic endocrinology.

Progesterone is naturally secreted by the corpus luteum and placenta. It is also synthesized by the adrenals and testes where it acts as a precursor of various steroid hormones. (Fig. 61.2)

Physiological functions of progesterone: The important physiological functions are:

(a) To induce the 'secretory phase' of the menstrual cycle;

(b) To promote the development of the alveolar (acinar) system of the breast;

(c) To prepare the endometrium for the implantation of the fertilized ovum and to induce decidual reaction;

(d) To induce changes in the vaginal epithelium and secretion, characteristic of progestational effect. These are described below.

(e) It also causes certain metabolic changes; prominent among these is the midcycle rise in basal body temperature (BBT) seen in human females. This rise is correlated with ovulation.

Bioassay of progestational activity: Various procedures are now available which are based on the technic used originally by Corner and Allen. In this method, an isolated female rabbit in estrous is castrated following the coitus and then given the unknown extract in divided doses for five days. The endometrium is then examined histologically for the degree of secretory changes induced. None of the assay technics, however, can give unequivocal estimate of the progestational activity of the newer synthetic compounds as some of them have estrogenic and androgenic properties as well.

Classification of progestins:

I. Progesterone

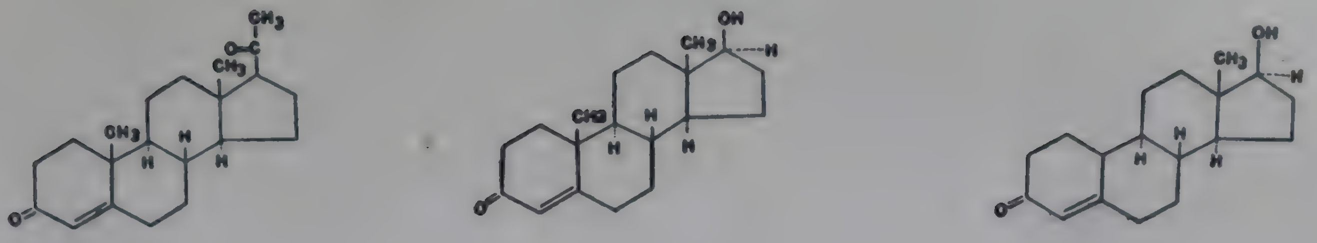
II. Derivatives of progesterone:

(a) Esters of 17-alpha hydroxyprogesterone such as caproate or acetate.

(b) C.6-substituted 17-alpha hydroxyprogesterone derivatives e.g. Medroxyprogesterone acetate, Megestrol and Chlormadinone acetate.

(c) Dehydrogesterone (Duphaston).

III. Derivatives of testosterone e.g. Ethisterone, Dimethisterone.



Progesterone

Testosterone

19 Nor-testosterone

Fig. 61.4

IV. Derivatives of 19-nor testosterone (testosterone without the 19-methyl group Fig. 61.4) e.g. Norethisterone, Norethynodrel, Ethynodiol diacetate, Norgestrel and Lynestrenol.

The progestational actions of the testosterone derivatives are, in general, similar to those of progesterone except that they are modified by the associated estrogenic and/or androgenic properties of these compounds. Hence, progestins can also be classified on the basis of their biological characteristics:

I. Pure progestins e.g. Progesterone, Dehydrogesterone, Esters of 17-alpha hydroxyprogesterone, Chlormadinone and Megestrol.

II. True progestins with possible androgenic effects e.g. Medroxyprogesterone, Norgestrel.

III. Progestins with androgenic effects e.g. Norethisterone.

IV. Progestins with estrogenic effects e.g. Norethynodrol.

V. Steroids of uncertain status e.g. Ethynodiol diacetate.

Pharmacological actions of progestins:

(a) **Endometrium:** Progesterone, administered to the properly prepared (estrogen primed) patients, duplicates the changes of secretory phase of the menstrual cycle. Continuation of progestational therapy can prolong the luteal phase and induce decidual changes, characteristic of early pregnancy, in the endometrial stroma. With the newer progestins, particularly with testosterone derivatives and 19-nor compounds, however, the histological changes are not so classical, on account of their additional estrogenic and/or androgenic actions.

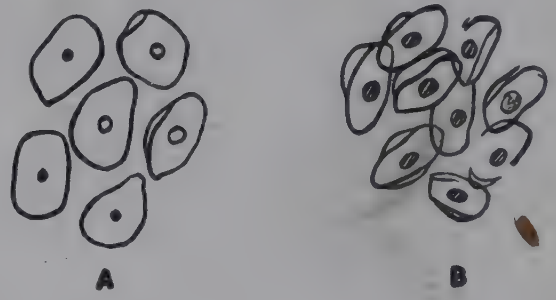


Fig. 61.5: Vaginal cytology

(A) Estrogenic effect

(B) Progestogenic effect

(b) **Vaginal epithelium and secretions:** Progesterone prevents cornification of the vaginal epithelium and brings about increased glycogen deposition. The epithelial cells show increased folding and elongation of nuclei (Fig. 61.5). Complete maturation of cells cannot take place and increased number of cells are desquamated. Thin, watery and profuse vaginal secretion, so characteristic of estrogenic action, becomes thick, viscid and scanty.

(c) **Mammary gland:** Exogenous progesterone can promote acinar growth in estrogen primed mammary gland.

(d) **Ovulation inhibition:** Progesterone inhibits ovulation only in large doses. The synthetic 19-nor testosterone derivatives are potent gonadotropin and ovulation inhibitors; this could as well be partly due to their inherent estrogenic activity.

(e) **Metabolic actions:** Exogenous progesterone can raise the BBT similar to that observed during the midcycle. Synthetic progestins-like testosterone derivatives and dehydrogesterone are not thermogenic.

Progesterone probably has some catabolic action and has been shown to promote nitrogen loss. It also promotes sodium and chloride loss. These actions are prominent in patients with adrenal insufficiency. Synthetic progestins, however, have no such consistent effects. Unlike estrogens, progestins in low doses produce no significant change in carbohydrate and lipid metabolism.

Progesterone has also been shown to increase respiratory activity and to produce a fall in alveolar pCO_2. Synthetic progestins lack this action.

(f) **Maintenance of pregnancy:** Natural progesterone is believed to help in the maintenance of pregnancy, although it is not definitely proved. In *in vitro* studies, progesterone exerts a blocking effect on uterine contraction.

(g) **Antineoplastic action:** There is some evidence to indicate that progesterone can suppress estrogen induced fibromyomata in animals. Progestins have been used to treat advanced cancer of the breast and the endometrium.

(h) **Other actions:** Some of the synthetic progestins have associated estrogenic, androgenic and/or anabolic actions (Table 61.1).

Absorption, fate and excretion: Progesterone is not effective orally, probably owing to metabolic degradation during its passage through the liver. Further, it has a relatively short biological half-life. Given by injection in oily solution, it is rapidly absorbed and inactivated in the liver. Metabolic products are numerous. Of these, pregnanediol, which is conjugated with glucuronic acid and excreted in the urine, is frequently used as an indicator of progesterone secretion. The rate of turnover of progesterone in the body is very rapid. Although some other metabolites are also excreted in the urine, estimation of pregnanediol gives valuable information regarding progesterone secretion. Majority of the newer progestins are effective orally as they are not easily destroyed during their passage through the liver. They are mainly metabolized in the liver.

Adverse reactions: Apart from their pharmacological actions which may modify the menstrual cycle and decrease the flow, progestins, in general, are relatively safe drugs. Derivatives of testosterone and 19-nor testosterone can cause nausea, breast discomfort, headache, fatigue, mental depression and rarely liver damage.

It must be noted that some of the synthetic progestins such as norethisterone may cause androgenic actions on developing female foetus and hence, should not be employed during pregnancy. For the same reason, they may cause weight gain, acne and hirsutism.

Preparations and dosage: These are given in Table 61.1.

Therapeutic uses of progestins:

(1) **Functional uterine bleeding:** This is commonly due to anovulatory cycles and is frequently a cause of irregular and/or excessive bleeding in young girls at the time of menarche and in elderly women approaching the menopause. Progestins are specific for this condition. Norethisterone given in doses of 5-10 mg. 4-6 hourly will stop the bleeding within 24 hours. It is usually continued in doses of 5 mg. twice daily for 1-2 weeks; following its withdrawal, the normal menstrual flow may ensue. In order to prevent excessive bleeding, progesterone or its derivatives are administered from 15-25th day of the menstrual cycle. Other progestins with some estrogenic action are also equally effective. Frequent irregular bleeding calls for the treatment with estrogen-progestin combination from 5th to 25th day of the cycle. Such repeated cyclic treatment may ultimately help to control and regulate the menstrual cycles in young girls until

Table 61.1: **Progestins in Current Use**

Preparation	Supplied as	Dosage**	Remarks
Progesterone I.P.	Tab. 10 and 25 mg. Inj. 10 to 25 mg./ml.	Functional uterine bleeding: 5 to 10 mg. I.M. daily; habitual abortion: 1-2 mg. daily; threatened abortion: 5-10 mg. daily.	Mildly catabolic.
Derivatives of progesterone:			
Hydroxyprogesterone caproate (Proluton depot)	Inj. 125 and 250 mg./ml.	Threatened and habitual abortion: 125 to 500 mg. weekly I.M.; functional uterine bleeding: same dose.	Mildly catabolic, long acting (8-14 days).
*Medroxyprogesterone acetate (Provera)	Tab. 2.5 and 10 mg. Inj. 50 mg./ml.	Functional uterine bleeding: 2.5 to 10 mg. daily; threatened and habitual abortion: 10-40 mg. daily orally or 50 to 100 mg. I.M. weekly.	Mildly catabolic.
Dehydrogesterone (Duphaston)	Tab. 5 mg.	Dysmenorrhoea: 10 to 25 mg. daily; same dose also used in threatened abortion and in functional uterine bleeding; in endometriosis: 30 mg. daily.	Does not inhibit ovulation. Mildly catabolic.
Allylestrenol (Gestanin)	Tab. 5 mg.	Threatened and habitual abortion: 10-20 mg. daily; premenstrual tension: 5-15 mg. daily.	
*Chlormadinone acetate	Tab. 2 mg.	2 to 6 mg. in the conditions mentioned above.	
Megestrol		Used in oral contraceptive combination pills.	
Derivatives of testosterone:			
Ethisterone I.P.	Tab. 25 mg.	25 to 100 mg. orally or sublingually.	Mildly estrogenic and androgenic.
*Dimethisterone	Tab. 5 mg.	15 mg. daily.	Mildly estrogenic.
Derivatives of 19 nor-testosterone:			
*Norethisterone (Primolut N)	Tab. 1, 2 and 5 mg.	Primary and secondary amenorrhoea: 5-15 mg. daily; functional uterine bleeding: 10-30 mg. daily; endometriosis: 20-30 mg. daily; same dose is also used in the treatment of premenstrual tension and for the relief of dysmenorrhoea.	Androgenic and anabolic actions.
*Norethisterone acetate	Tab. 5 and 10 mg.	2.5 to 15 mg. daily. Indications similar as norethisterone.	Mildly androgenic and anabolic.
*Norethynodrel	Tab. 5 and 10 mg.	Primary and secondary amenorrhoea: 5 to 10 mg. daily; endometriosis: 20 to 30 mg. daily.	Estrogenic.
*Ethynodiol diacetate	Tab. 1, 2 mg.	Functional uterine bleeding: 1 to 2 mg. daily; endometriosis: 4 mg. daily.	More potent than ethisterone; estrogenic, anabolic.
Lynestrenol (orgametril)	Tab. 0.5 mg.	5-10 mg. daily.	

*Also used as oral contraceptive.

**For various regimen details, see the text.

sufficient endogenous steroid levels are achieved.

(2) **Dysmenorrhea:** Some women complain of either discomfort or pain (either dull or colicky) in the lower abdomen before or during menstruation. The pain may be mild to incapacitating in its intensity. This 'dysmenorrhea' is only a symptom and not a complete diagnosis. It is common in the teenagers but also occurs in the older women. Before starting drug treatment, one should make certain that an intrauterine contraceptive device is not responsible for this symptom.

The cause of the primary, *spasmodic dysmenorrhoea* of the teenager is not known but it generally disappears with increasing age. Most girls with this symptom are helped by physical exercise, explanation, reassurance and analgesics such as aspirin, paracetamol and codeine, given either alone or togther with an anticholinergic drug like atropine. Marriage and pregnancy should not be suggested as cures for this condition. When the symptom is severe and incapacitating, it can be abolished by inhibiting ovulation with an estrogen or with 'a combination pill' given daily from 5th to 25th day of the menstrual cycle for 4-6 cycles. While dispensing such pills to unmarried girls, care should be taken not to label the container as 'contraceptive pills'. In most cases, the symptom does not recur after stopping the treatment. If inhibition of ovulation is considered undesirable for some reason, oral dydrogesterone (which is more expensive) may be used from 8th to 25th day of cycle in the dose of 10 mg twice a day.

Patients not responding to the above therapy and all older women with *secondary dysmenorrhea* need careful gynaecological investigation to exclude local lesions such as endometriosis, fibroids and infection. Dysmenorrhoea may be a presenting symptom in pelvic tuberculosis. In all such cases the treatment of the cause is important.

Membranous dysmenorrhea is rare and often familial. The menstrual endometrium is painfully shed in large strips or even as a complete cast. Although the oral pills can be used to treat these cases the results are less rewarding; curettage is also unhelpful. Norethisterone 10 mg. daily given for five, immediately premenstrual days may produce beneficial effects in some patients.

(3) **Amenorrhea:** Progestins will act in this condition only if the endometrium is primed with an estrogen. The treatment of amenorrhea is discussed elsewhere.

(4) **Endometriosis:** Oral progestins, given continuously, are highly effective in this condition. They cause marked regression of the endometrium. Norethisterone can be used daily in doses of 20 mg. increasing by 10 mg. daily if vaginal spotting occurs. Amenorrhoea can be maintained by 40-60 mg. daily dose for 3 to 9 months depending upon the severity of the case.

(5) **Habitual abortion:** Evidence for therapeutic usefulness of progesterone in threatened or habitual abortion is equivocal.

(6) **Diagnosis of pregnancy:** Progesterone is used in combination with estrogen in secondary amenorrhea suspected to be due to pregnancy. Following the administration of this combination, withdrawal bleeding would occur in case of amenorrhea not due to pregnancy.

(7) **As oral contraceptives:** This is one of the most important uses of progestins and is discussed in Chapter 62.

(8) **Miscellaneous uses:** Medroxyprogesterone has been found useful in treating children with precocious puberty. It acts by inhibiting the pituitary gonadotropin liberation and has to be used regularly for several years until the time is opportune for allowing the child to mature sexually.

Progestins can be used to prolong the luteal phase of the menstrual cycle and thus to postpone the onset of menstruation. Norethisterone in the oral dose of 5 mg. daily is adequate if the subject comes early in the second half of the menstrual cycle. If, however, she seeks advice only a few days before the due date, higher doses (5-10 mg t.i.d.) are needed. Some women may not tolerate such high doses of norethisterone, orally; in that case, hydroxyprogesterone caproate (250 mg i.m.) along with small oral doses of norethisterone is recommended.

Progestins are also used in the treatment of endometrial carcinoma (see Chapter 65).

62 Antifertility Agents and Ovulation Inducing Drugs

Like other animals, man has a natural desire to reproduce his kind. However, unlike animals, he alone can control the reproduction at will and plan his family. Man's great reproductive potential and the greatly increased survival rate in recent years have posed a major problem of population growth with far reaching consequences. According to the United Nations estimate, at the present rate of growth, the world population is expected to double in 35 years and it would be eightfold in a century. If the world resources are considered, this forecasts a disaster for the human race, unless the fertility is controlled. As for India, the equivalent of the entire population of Australia is added every year! Fertility control is very essential for maintaining satisfactory standards of living and for raising the existing standards in developing countries. Furthermore, it is equally important for family planning which is defined as "the limitation of spacing of births in the best interests of the mother, the child and the rest of the family." The problem is essentially interdisciplinary and can only be solved by the concentrated efforts by biologists, sociologists and educationists; the use of pharmaceutical agents for this purpose is but one aspect of the whole programme.

Physiology of human reproduction: The reproductive cycle in the human, in which ovulation is a key event, is the result of the interplay of the hypothalamus, the pituitary and the ovaries. With respect to ovulation, female mammals can be divided into two groups:

(1) *Reflex ovulators*, e.g. rabbits, cats, ferrets and minks in whom the sensory stimulus of mating or electrical stimulation of cervix induces ovulation, and (2) *Spontaneous ovulators* like cows, monkeys, women, in whom follicular rupture occurs in the absence of any immediate sensory stimulus.

At the time of puberty, the human ovary contains thousands of immature follicles of which only about 400 mature during the reproductive life of about 30 years. Of these, only a few can get fertilized and lead to successful pregnancies.

Under the influence of pituitary FSH, the Graffian follicle matures and considerable amounts of estrogen are produced. The sudden midcycle spurt of luteinizing hormone (LH) is followed by ovulation (rupture of the mature follicle) liberating the ovum. Ovulation usually occurs on day 14 (± 2) of a 28 day cycle. The oocyte enters the fallopian tube and within 12 hours it reaches the ampullary region where it can be fertilized by the sperm. By 18th day of the cycle, the fertilized ovum is converted into a blastocyst which reaches the cavity of the uterus. By 21st—23rd day of the cycle, the blastocyst begins to get implanted (nidation) beneath the surface of the uterine endometrium. The implantation stage is completed by 35th day from the first day of the last menstrual period; at this time the fetal placental circulation starts developing. This means that pregnancy may be considered as existing only 5 weeks after the onset of last menstrual cycle.

Ovulation may be judged by noting changes in the cervical mucus, vaginal cytology, endometrial biopsy and a rise in basal body temperature. All these changes reflect the production of progesterone by the corpus luteum.

The cervical mucus is an alkaline gel, rich in protein and fructose. During the follicular phase it is clear, thin, copious, acellular and somewhat elastic. This property permits the mucus to be stretched into threads from 5 to 15 cm. in length. Because of the presence of abundant sodium and potassium chloride, the mucus assumes a characteristic fern-like pattern when dried on a glass slide. Clinically, ferning and 'thread test' (spinnbarkeit) are utilized to judge the estrogen influence. Just before the ovulation, its consistency is believed to be most ideal for the transport of sperms into the uterus. Soon after the ovulation, under the influence of progesterone, the cervical mucus becomes tough, viscous and translucent and the sperms may find it difficult to penetrate it. The ferning disappears and it cannot be stretched without breaking. Some women may experience unilateral low abdominal pain at approximately midcycle; this is attributed to the occurrence of ovulation.

Although all these parameters are useful clinically, none of these can be considered as a definite evidence of ovulation. The only definite evidence of ovulation is either recovery of the ovum or pregnancy.

Extrahypothalamic regions of the CNS, acting via the hypothalamus, exert a modulating influence on ovulation. There is evidence to suggest that the menstrual rhythm and probably ovulation in the human female are influenced by emotional and environmental factors. Thus, irregular menstrual periods are known in nurses on night duty, and air hostesses travelling great distances.

The exact duration of survival of sperms in the vagina is not known but is believed to be about 1-2 hours while they can remain active in the cervix and uterine cavity for about 45-50 hours. It is believed that sperms can get into the uterine cavity immediately after the coitus because of uterine contractions which help to suck the fluid containing the sperms from the vagina.

Apart from the coitus interruptus, theoretically, the fertility control can be achieved by:

(1) Controlling central mechanism,

(2) Preventing the union of sperm with ovum, by using physical or chemical barriers, and

(3) By using drugs that modify the physiological mechanisms of reproduction.

Since the hypothalamus is known to play an important role in controlling the secretion of pituitary gonadotropins, emotional factors and certain drugs acting on the hypothalamus can block or induce ovulation by modifying the secretion of gonadotropin releasing factors. Thus, lactation amenorrhea due to suckling reflex and amenorrhea in young women due to stress are known. Tranquilizers like chlorpromazine and reserpine have been shown to modify the menstrual cycle in women; and suppression of menses following hypnosis has also been reported. However, the practical application of such procedures for the control of reproduction appears to be very remote at present.

Birth control by using physical and/or chemical barriers to prevent the union of sperm with ovum is not new. In the Ebers Papyrus of 1550 B.C., the preparation of a tampon treated with a spermicide has been described; and Arabs were using some intra-uterine foreign body to prevent the conception in saddled camels for ages. Presently, various physical barriers like condoms, pessaries or intrauterine loops and chemical barriers in the form of spermicidal gels and foam tablets are used. Such spermicides are simple to use and involve less genital manipulation. These methods, however, are not very reliable and often inconvenient to practice. No doubt, some of these like condoms and IUCD have definite points in favour for their use: (i) they are cheap, and (ii) they require no planned programme or continued effort as is necessary in the case of oral contraceptives.

Fertility can be controlled by using drugs which can act by the following mechanisms:

(a) Inhibition of ovulation;

(b) Modifying the cervical mucus;

(c) Slowing down the rate of egg transport;

(d) Preventing the ovum maturation and sperm capacitation;

(e) Interfering with the implantation;

(f) By immunological methods; and

(g) Inhibiting spermatogenesis in males.

The drugs which are now in use act mainly by the first two mechanisms and are discussed below.

Oral contraception is a highly effective and acceptable method. In this method. either an estrogen-progestin combination or a progestin alone is used.

ESTROGEN-PROGESTIN COMBINATION

Since the first clinical demonstration of usefulness of such an oral combination for contraception by Pincus (1955), various commercial preparations have been tried extensively. Some of those currently available in India are given in the Table 62.1 The remarkable efficacy and the relative safety of these compounds along with the ease of their administration have made them quite popular. These preparations contain ethinylestradiol or its 3-methyl ether (mestranol) as estrogen and a progestin, either belonging to 19-nor testosterone group or derived from progesterone.

Methods of administration:

(1) The commonest procedure is to administer one pill containing both estrogen and progestin (Table 62.1) daily, orally, from 5th day to 25th day of the 28 day cycle. This is the most effective type of oral contraception currently available.

(2) In the sequential regimen estrogens are given daily, orally, from 5th to 20th day followed by estrogen-progestin combination from 21st to 25th day. Inhibition of ovulation, in this case, is due to estrogen alone and progestin is added to ensure satisfactory withdrawal bleeding. This 'pill' is not as effective as the combination type. Its use is accompanied by more frequent adverse effects, and the risk of pregnancy is twice as high as with the combination 'pill'.

(3) In the serial method, the woman is given a pack consisting of 16 estrogen, 5 estrogen/progestin and 7 placebo tablets. The treatment consists of taking a pill daily in the order mentioned. No break is permitted in this method. This may avoid any confusion in taking the tablets correctly for specified periods in sequential regimen.

(4) Monthly estrogen-progestin injection: Recently, 17-alpha dihydroprogesterone acetophenone, a long acting progestational agent, administered I.M., once a month, in the dose of 150 mg. along with 10 mg. of estradiol enanthate, has been shown to prevent conception. The probable advantage of such a preparation is that it is given only once a month.

Mechanism of action: The mechanism of the contraceptive action of these agents is complex. It appears, however, that the combination type suppresses both FSH rise and LH peak observed during the normal menstrual cycle probably by inhibiting the release of LH-RH. Thus, follicular growth is not initiated and ovulation does not occur.

Estrogen alone can be effective but given alone is not suitable as it causes profuse irregular bleeding. The addition of a progestin increases the certainty of contraceptive effect, prevents break-through bleeding and ensures predictable withdrawal bleeding at the end of the cycle. Furthermore, the progestin may also help by modifying the cervical mucus. The ovulation inhibitory action of progestin varies with the type of compound used and the dosage, being more marked with progestins derived from 19-nortestosterone. Certain progestins may prevent ovulation, in part by a direct action on the ovary. It is interesting to note that certain 19-norsteroid compounds are metabolized in the body to produce sufficient ethinylestradiol to account for their ovulation inhibiting effect.

In case of the sequential type, the estrogen suppresses the FSH rise but stimulates LH secretion giving rise to unusual multiple LH peaks. This therapy therefore, prevents ovulation probably by suppressing the early FSH rise and the resultant initiation of follicle growth.

Pharmacological actions: The detailed pharmacological actions of estrogen and progesterone are described earlier. Only the effects relevant to their contraceptive action are described below:

(a) **Endometrium:** The effect produced by the combined hormone therapy is similar to that of 'luteal phase'. The full secretory activity of the endometrial glands is achieved within 3-4 days of starting these pills, leading to predecidual changes. Later, the endometrium becomes thin and hypoplastic. The changes are reversed 2-3 months after stoppage of treatment. In the case of sequential method, 'follicular phase' is seen during the estrogen administration with incomplete 'luteal phase' following the addition of progestin. Continuous administration of a progestin in the combined regime increases the thick cervical mucus, causing a 'cervical barrier' hostile to sperm penetration.

(b) **Pituitary/ovarian axis:** Prolonged administration of these drugs does not seem to cause any permanent structural changes in the pituitary or ovary, although during therapy ovaries may appear smaller and their secretion may practically cease.

(c) **Metabolic effects:** Many investigators have reported hyperglycemia, glycosuria and mildly impaired glucose tolerance, along with a rise in the post-absorptive serum immunoreactive insulin levels in women taking the pills. However, an increased incidence of clinical diabetes mellitus has not yet been established. The mechanism of these abnormalities is not clearly defined but is believed to be an increased peripheral resistance to the hypoglycemic action of insulin. The pill also causes a slight increase in plasma lipids particularly triglycerides in many women.

(d) **Other endocrine glands:** As in pregnancy, the plasma protein bound iodine (PBI) is raised due to a greater binding capacity of thyroxine binding globulin. There is also an increase in the cortisol binding globulin, transcortin. Changes in cortisol metabolism with a slight but definite rise in the free plasma cortisol level and a reduction in the rate of cortisol inactivation have been reported. This may be responsible for fluid retention, headache and neuropsychiatric disturbances sometimes observed during combination pill therapy.

Adverse reactions:

(1) **General toxicity:** Gastrointestinal symptoms like nausea, anorexia and vomiting are common and are due to the estrogen component. The drug should be taken at bedtime on a full stomach to minimise them. The estrogen may also be responsible for other effects like fluid retention, breast engorgement, mastalgia, chloasma and increased vaginal secretion (leucorrhea). Excessive estrogen also suppresses lactation.

Although the compounds belonging to 19-nortestosterone group have androgenic actions, the latter are rarely evident with therapeutic doses. However, there is some chance of masculinization of a female fetus, if preparations containing 19-norsteroids are taken during pregnancy. In certain individuals, the anabolic action of these compounds is seen in the form of weight gain. In others, the weight gain is due to sodium retention and edema and is mostly due to estrogens. Blurring of vision and mental depression have also been reported; the latter can be serious enough to cause suicidal tendencies and the risk is greater in women with past history of depression. This depression appears to be related to estrogen-induced alteration in vitamin B_6 metabolism.

The hepatic abnormalities induced are usually reversible and are basically alterations in the bile-secreting function of the hepatocytes (cholestatic). Usually, the 'pill' produces no clinical problem, but a substantial number of women have abnormal liver function tests in the absence of symptoms. Only a few women develop a clinical cholestatic jaundice. Usually, a woman who has had jaundice during pregnancy is more prone to develop jaundice while taking the pill and vice versa. A previous history of jaundice is not a contraindication to oral contraceptives. But, if a woman on the 'pill' develops acute hepatitis the drug should be stopped and should be resumed only after the liver function tests have been normal for at least six months. Women most likely to develop abnormalities of glucose tolerance are those with abnormal G.T.C. during earlier pregnancies, older women, those who have had infants with birth weights more than 8 lbs. and those who gain excessive weight while on the pill. The changes are usually reversible on stoppage of pill.

The 'pill' has been reported to cause rheumatic symptoms and to induce serological abnormalities in a few cases and it is advisable that patients with lupus erythematosus should avoid the pill. The 'pill' decreases the serum levels of pyridoxine, folic acid, vitamin C, calcium and zinc whereas those of vitamin A, copper and iron are elevated.

(2) **Bleeding irregularities:** Cycle control is usually excellent. Sometimes, however, bleeding similar to that of a normal menstrual period occurs during the course of medication. In such cases, the dose of estrogen may be increased, alternatively, the tablets are stopped and a new course started five days later with a preparation containing larger quantity of progestin. 'Spotting' is characterised by intermittent blood-stained trickling during the therapy and is usually due to failure to take the pills regularly. Its incidence appears to be higher with low estrogen or no estrogen pills. Occasionally, temporary amenorrhea for 1-2 cycles may occur and is of no significance.

It should be noted that the onset of the first menstruation following stoppage of the 'pill' may be delayed for 6-8 weeks. Informing the patient about this in advance can spare her many anxious days. Prolonged amenorrhoea for years, though rare, is certainly a disquietening feature of this therapy. The use of the oral combined 'pill' should be avoided in women who have oligomenorrhea or amenorrhea.

(3) **Thromboembolic phenomena:** There appears to be a definite relationship between the use of oral contraceptives and the incidence of deep vein thrombosis, cerebral thrombosis and pulmonary embolism. This is related to the concentration of the estrogen component. A dose of 50 μg. of ethinyl estradiol seems to be the safe upper limit beyond which the risk increases. A similar risk is also present in normal pregnancy. In women on the pill, a complaint like persistent headache should not be treated lightly as it may be a warning of an impending cerebrovascular accident. The pill is contraindicated in "patients with thrombophlebitis, thromboembolic disorders, cerebral apoplexy or with a past history of these conditions." The appearance of any of these or of vascular headaches, leg cramps, visual disturbances or hypertension is an indication for permanent discontinuation of the pill. Oral contraceptives probably do not cause true migraine; but latent migraine may be unmasked and an existing attack aggravated.

(4) **Hypertension:** The reported incidence of hypertension has been as high as 15%. It is reversible within about three months of the discontinuation of the medication and is probably due to the estrogen induced increase in plasma renin-substrate (angiotensinogen). Before treating the hypertension in a female patient, 'contraceptive pill' as a cause should be ruled out.

(5) **Uterine fibroids:** Uterine fibromyomata can undergo enlargement during therapy with pills; the presence of fibroids is a relative contraindication to such therapy.

(6) **Carcinogenicity:** Although estrogens are known to be cancinogenic in animals, experience of the last 20 years has not revealed any such risk following prolonged administration of these pills to human females. They should not be used, however, in the presence of estrogen dependent malignancies, such as breast cancer, in Hodgkin's disease and in malignant melanoma. Further, it is a wise

precaution to examine the breasts and the cervical smear for malignancy before starting the treatment and then periodically during the therapy.

It must be noted that in general these pills appear to be fairly safe, highly effective and acceptable. Usually, they do not affect the libido; in fact, the removal of the fear of pregnancy may greatly improve the sexual as well as the marital relationship. Subsequent fertility is not affected either. However, the cost and the necessity of following a strict regimen make the acceptance of these drugs as the sole method of contraception difficult, particularly in countries where both poverty and illiteracy are rampant. Further, these hormones lack specificity in that they also affect other tissues in the body and alter various metabolic processes. The single daily dose regime does not assure a constant blood level throughout the day; on the other hand, it is likely that the same dose is too large for some women.

Before starting the pill, it is essential to go through the personal history and to carry out a detailed examination to exclude any medical contraindication. After the start of oral contraceptives, the woman should be initially seen during the second or third cycle of medication in order to check that all is well and that she really understands how to take the drug. Thereafter, she may be called after 6 months and still later annually. The observations should include the following: (a) blood pressure and weight, (b) liver function and glycosuria, (c) cervical and breast abnormalities, (d) evidence for thrombophlebitis, (e) changes in the retinal blood vessels and (f) mental changes. Since the pill is capable of causing various systemic effects, a history of taking the pill should form a part of the routine medical history in women of the child-bearing age and this information should be made available to any other doctor to whom the case may be referred.

In general, the 'pill' should not be prescribed to a young unmarried woman for regularising her irregular cycles as after its stoppage, prolonged amenorrhea may occur and conception may be prevented due to anovulation. It is also advisable to stop the pill for 1-2 months before any elective surgery, since it increases the vascularity and causes edema of the tissue. Further, deep vein thrombosis is more common in the post-operative period.

The incidence of adverse effects with the same combination may vary from place to place and from observer to observer. The results are influenced by such factors as patient selection, motivation, socio-economic or demographic influences, nutrition and other habits. Hence, it is difficult to choose from among the various combinations available purely on the basis of 'fewer' adverse effects.

The effectiveness of oral anticoagulants such as warfarin may reduce in patients taking contraceptive steroids. Further, such subjects can be relatively resistant to the effects of the tricyclic antidepressants. Breakthrough bleeding and failure of contraceptive therapy has been noted in subjects taking anticonvulsant drugs like diphenylhydantoin and certain antibiotics like rifampicin.

Preparations: From the therapeutic point of view, the combination pills available commercially can be grouped into those which are *strongly progestogenic* and those which are *weakly progestogenic* in action. Compared on weight basis, the activities of various synthetic progestins differ markedly as some of these compounds are not as easily metabolised as norethisterone given orally. Thus, in their progestogenic activity 1 mg. each of norethisterone acetate, ethynodiol diacetate and norgestrel are almost twice, 15 times and 30 times as active as 1 mg. of norethisterone, respectively. However, in practice the net pharmacological effect produced by a 'combination pill' probably depends upon the relative progestogenic, estrogenic and androgenic properties of its individual constituents (Table 62.1). Since

Table 62.1: **Comparative Biologic Properties of Synthetic Progestins in Experimental Studies**

Properties	Norethisterone	Norethisterone acetate	Norethynodrel	Ethinodiol diacetate	Norgestrel
Progestogenic	++	++	++	+++	++++
Estrogenic	—	—	+++	++	—
Antiestrogenic	+	+	—	?	++
Androgenic	++	++	—	+	+++

the same combinations are also useful in controlling certain menstrual disorders, in a woman with an associated menstrual irregularity, a proper combination can be selected. Thus, premenstrual tension, edema, cyclic weight gain, irregular bleeding and heavy periods suggest an estrogen excess which can be countered by the strongly progestogenic pill, while a patient with excessive acne, hirsuitism, abdominal and leg cramps, and scanty vaginal secretions may benefit from a less progestogenic combination (Table 62.2). Of course, in women with normal menstrual cycles, a combination containing 0.03-0.05 mg of ethinyl estradiol with the minimum effective dose of a progestin is preferred. The incidence of 'spotting' appears to be higher with low-estrogen (0.02-0.03 mg) pills.

Table 62.2: **Some Combination Types of Oral Contraceptives**

Name	Progestin (mg)
With ethynyl estradiol 0.03 *mg.*	
Microgynon	Norgestrel (0.15)
Eugynon	-do- (0.25)
Primovalar 30	-do (0.50)
With ethinyl estradiol 0.05 *mg and less progestogenic*	
Eugynon 50	Norgestrel (0.25)
Ortho-Novin	Norethisterone (1.0)
Minovlar ED	Norethisterone acetate (1.0)
Orlest 28	
Lyndiol 1 mg	Lynestrenol (1.0)
Noracycline	
With ethinyl estradiol 0.05 *mg and more progestogenic*	
Anovlar 21	Norethisterone acetate (4.0)
Gynovlar 21	-do- (3.0)
Norlestrin	-do- (2.5)
Voldys 21	Megastrol acetate* (4.0)
Lyndiol 2.5 mg	Lynestrenol (2.5)
Ovulen 50	Ethynodiol diacetate (1.0)
Primovlar 50	Norgestrel (0.5)
Ovral	

*Derivative of 17-alpha acetoxyprogesterone. Others are all derivatives of 19-nortestosterone.

Pill-induced depression may respond to vitamin B_6 in the dose of 20 mg. twice a day. If it fails, the pill should be discontinued.

PROGESTINS AS CONTRACEPTIVES

CHLORMADINONE ACETATE: This is an analogue of medroxyprogesterone with progestational properties. Given in small doses of 0.5 mg. daily, the drug produces inhibitory effect on cervical mucus. Larger doses can influence the endometrium and inhibit ovulation.

It is interesting to note that chlormadinone alone, when given orally, daily, continuously, in doses of 0.5 mg. can act as an effective contraceptive, without affecting the ovulation or the endogenous hormonal control of cyclic bleeding. It is effective during the lactation period without suppressing the lactation.

The exact mechanism of action of this compound is not known. The small doses used, however, do not seem to suppress the LH peak. It has antiestrogenic properties on endometrium and cervical mucus which becomes thicker, tough, cellular and hostile to sperm penetration.

The important adverse effects include nausea, headache and breakthrough bleeding. A few beagles treated with chlormadinone developed breast nodules and hence, the drug has been withdrawn.

NORGESTREL: This is a 19-nortestosterone compound with very potent progestational activity. Given alone in the daily oral dose of 50-75 μg. continuously, it can prevent conception. The drug probably acts by several mechanisms. It reduces the sperm penetrability of the cervical mucus and impairs luteal function. It causes irregular and generally short bleeding intervals in a high proportion of cases. Other adverse effects are slight and appear to be tolerable. The drug is also used in combination pills.

MEDROXYPROGESTERONE ACETATE (Provera): This is a potent progestational compound, which is effective both orally and parenterally. It has also been used as an oral contraceptive, given along with an estrogen, by the sequential method. Unlike 19-norcompounds, it is not metabolised to estrogen in the body. Although it has been shown to possess foetal masculinizing activity in animals, no such effect has so far been observed in humans. There is some evidence to suggest that the drug causes malignant breast nodules in beagles and may predispose to cervical cancer.

The long acting, slowly absorbed, intramuscular preparation of this compound (Depot-Provera) has been tested for its contraceptive activity. Given alone, intramuscularly, in doses of 150 mg. every three months, the drug can effectively control fertility. It has been demonstrated that the pharmacological action of a single dose of 150 mg. of medroxyprogesterone lasts for 13 to 41 weeks. The major adverse effects include complete disorganization of the menstrual pattern, irregular bleeding and amenorrhea in a large proportion of cases. Some women have amenorrhoea for years and become obese following this therapy.

The mechanism of action of this drug as a contraceptive is not known but it inhibits the release of luteinizing hormone (LH) responsible for ovulation.

Although the drug needs further detailed evaluation, it has prompted the interesting possibility of controlling fertility over a longer period by one single injection. The preparation has been used for contraception during the post partum period where amenorrhoea for 6 months is not much of a problem.

It should be pointed out that the use of a progestin alone for contraception is much less reliable than that of estrogen-progestin combination and the incidence of annoying adverse effects may be high. Hence, the 'progestin-only' pills are currently used only in patients with a specific contraindication to estrogens and who find other contraceptive measures unacceptable.

Other methods: Most of the oral contraceptives currently in use act by inhibiting ovulation. However, fertility can be controlled by other methods that allow normal ovulation. The various mechanisms by which this can be achieved have already been mentioned; so far, drugs having such a selective effect on egg transport, ovum maturation and implantation without any uterotropic effect are not available.

A possible method of contraception by preventing implantation of the fertilized ovum offers some attractive features; such a compound need not be taken daily but only after coitus or when the periods are overdue. Thus, the user is expected to take such 'post-coital' or 'morning-after' pill for a period of 1-5 days following the intercourse to prevent pregnancy. It must be realized, however, that this could amount to almost continuous therapy in a portion of the population. An estrogen given in large doses for 4-6 days after the intercourse may prevent implantation. An ideal anti-implantation drug in women, however, is not yet available.

Among the various methods of contraceptions available today, none can be considered as absolutely safe, 100%

effective and ideal in all circumstances. In a given individual, one method can be considered better than the others. Hence, it is better to have a 'cafeteria type' approach, where the woman concerned is allowed to choose the method after being adequately informed about the various procedures available. Further, it is important to note, as pointed out by Sir Allen Parkes, that "the concentration of modern thought on technique should not obscure the fact that much depends on the relations between the man and the woman. A happy, knowledgeable and communicating couple, especially if they have a sense of humour, can get along with almost any method. It is the non-communicating couple for whom methods not contemporaneous with coitus are especially useful." Women who cannot be relied upon to take pills regularly and are likely to omit them often should be advised methods such as I.U.D. or surgical sterilization.

All the oral contraceptive drugs presently in use are to be taken by females. There is no reason why similar preparations should not be made available to be taken by males, which could act by inhibiting spermatogenesis. Spermatogenesis can be inhibited by androgens, estrogens and progestins. Although steroid compounds without excess of androgenic or anabolic activities are now available which inhibit spermatogenesis in experimental animals such compounds have not been clinically useful. One of the difficulties is that such hormonal inhibition in male may cause loss of libidinal drive which, even if psychic, may have damaging effect on the personality of the individual. Further, as pointed out by Petrow, "It is the woman who has the baby, and it is the woman who must have the assurance on effective control. On a somewhat lighter plane, it is difficult to believe that many women would accept a categorical statement by a man that he had taken his family planning pills for the past two months without fail. Men are notoriously unwilling to submit to medication discipline and the failure rate could well be high." Of course, vasectomy, carried out in properly selected cases, would be the most economical, reliable and relatively safe procedure for the males.

OVULATION INDUCING DRUGS

The problem of infertility is a joint one and both the partners need detailed examination. The male should be examined first. This is essential even if one decides to treat the female by newer fertility drugs. The treatment of male infertility is, at present, generally disappointing.

The largest single cause of infertility in young females is probably psychogenic, affecting the hypothalamic function. In some of these cases, psychiatric therapy may be helpful while in others adoption could itself be a psychotherapeutic measure.

The drug therapy of infertility due to ovulatory failure was till recently empirical and disappointing. Various measures such as wedge resection of polycystic ovaries, glucocorticoids, thyroid medication and radiation of the pituitary were employed with varying and unpredictable success. Before giving credit to any such therapy, it should be remembered that 20-35% of cases of infertility ovulate spontaneously.

Deficiency of the thyroid hormone is an uncommon cause probably responsible in less than 3% of anovulatory cycles. The results of thyroid medication in euthyroid anovulatory women are not at all convincing.

As mentioned in Chapter 61, estrogens may be responsible in triggering an ovarian signal for LH release. Estrogen administration has been demonstrated to cause LH release in rodents, monkeys and women, usually after a preceding period of LH suppression. Hence, low dosage of an estrogen may be useful in cases where some follicular activity is present but midcycle LH peak is lacking or corpus luteum is inadequate. An estrogen can be tried as pre-clomiphene medication or with clomiphene. Usually stilbestrol in doses of 0.1

mg. daily for first 3 days followed by 0.2 to 0.3 mg. daily for subsequent six days is administered from 5th to 14th day of the menstrual cycle.

Progestins are not useful except perhaps in patients with inadequate corpus luteum, endometriosis and in patients with persistent follicular function.

Glucocorticoids were found to be reasonably useful in hirsute amenorrheics and in women with polycystic ovarian syndrome with high normal or normal urinary 17-ketosteroids; this treatment was based on the finding that glucocorticoids suppress the adrenal overactivity in congenital adrenal hyperplasia by inhibiting excessive ACTH production. This results in ovulatory periods.

The introduction of ovulation inducing drugs marks a significant advance in the field of reproduction biology. These drugs are:

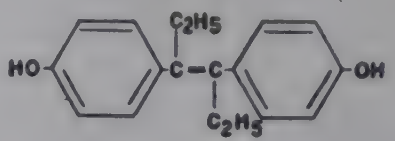
I. Synthetic LH-RH: Although this drug can induce ovulation in humans, it is not so useful therapeutically because of its short plasma half-life (less than 2 minutes after intravenous injection). A longer acting analogue may be more useful.

II. Human pituitary and chorionic gonadotropin combination as discussed in Chapter 61.

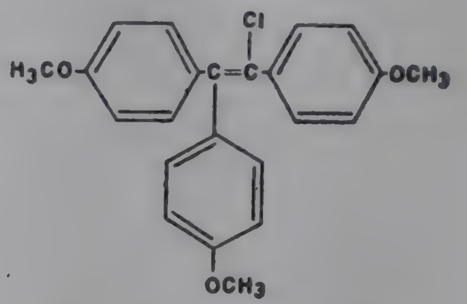
III. Antiestrogenic compound clomiphene citrate.

CLOMIPHENE CITRATE (Clomid, Fertyl): This is a triphenylethylene compound, with structural resemblance to stilbestrol and chlorotrianisene (Fig. 62.1). It was synthesized during the search for a potent estrogenic compound. But amazingly, the drug when tested in animals. was found to possess potent antiestrogenic and only weakly estrogenic actions. In rats, it stops the estrous cycle, decreases the secretion of gonadotropins and reduces the size of the ovary. In clinical trials, however, it proved effective in inducing ovulation in women with ovulatory failure.

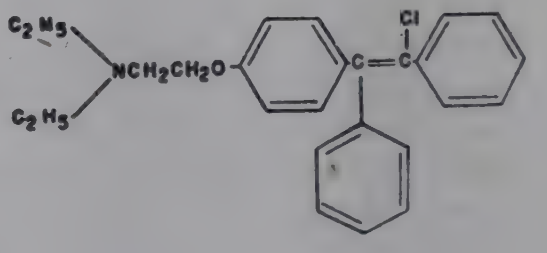
The commercially available clomiphene preparation contains both 'cys' as well as 'trans' forms. It is the 'cys' form which is closely related structurally to estrogens and is more potent than the racemic form.



Diethylstilbestrol



Chlorotrianisene (TACE)



Clomiphene

Fig. 62.1

Pharmacological actions:

(a) **Antiestrogenic action:** Clomiphene can produce regression of estrogen induced proliferative endometrium and can counter the keratinization of vaginal epithelium. It can prolong the luteal phase in normally menstruating women and nullify the ovulatory inhibition produced by contraceptive pills. Given to premenopausal women, it causes hot flushes.

It is probable that because of the structural similarity, the drug acts by competing with natural estrogen for common receptor sites in the uterus, the pituitary and the hypothalamus thus inducing the production and release of FSH and LH to cause ovulation. Recent electroencephalographic studies indicate that clomiphene probably acts on the hypothalamus to correct diencephalo-hypothalamic disturbances, of which failure to ovulate is one manifestation.

Following clomiphene, there is a marked increase in the urinary estrogens indicating stimulation of the ovaries. Although this could be due to increased gonadotropin secretion, a direct effect of the drug on ovaries cannot be ruled out. *In vitro* experiments have demonstrated that when clomiphene was added to human placental extract, it promoted the conversion of androgens to estrogens. Further, following clomiphene administration urinary gonadotropins are only moderately increased or remain unchanged and hence, cannot solely explain marked increase in the urinary estrogen output. Clomiphene, therefore, probably also has a direct effect on the ovary.

(b) **Gonadotropin stimulating action:** The drug stimulates the secretion of pituitary gonadotropins. In the presence of intact pituitary and responsive ovaries, the drug can induce ovulation. Since the drug is not effective in patients with marked decrease in endogenous estrogen production, it is postulated that clomiphene acts on the hypothalamo-pituitary axis either directly or indirectly through its antiestrogenic action which lowers the inhibitory influence of circulating estrogen.

(c) **Miscellaneous actions:** It has a weak estrogenic action.

Absorption, fate and excretion: The drug is well absorbed when given orally. It is concentrated in the bile and excreted in the intestines, from where it is reabsorbed. It is mainly excreted in the feces and only a small amount appears in the urine; half of the dose is excreted within 5 days.

Adverse reactions: Commonly, it causes hot flushes. The important drawback is that it causes ovarian enlargement and cyst formation due to overstimulation, which may lead to rupture and internal hemorrhage. Rarely, it can cause restlessness, blurring of vision and alopecia.

Therapeutic uses: (1) Clomiphene is mainly indicated in the treatment of infertility due to anovulation, as seen in dysfunctional uterine bleeding, polycystic ovarian disease (Stein-Leventhal syndrome), metropathia hemorrhagica and functional amenorrhea. In all these cases, adequate endogenous estrogenic activity must be present. Generally, the drug is given in daily doses of 50 mg. for 5-7 days. If there is no response, a second course may be given in the next cycle, with 100 mg. daily for 5-7 days. The drug should not be repeated if no response is seen in spite of 6 courses and the maximum total dose per cycle should be limited to 700 mg. Ovulation usually occurs 2-12 days after completion of the treatment. In case of an amenorrheic patient, the drug can be given at any time, while in those with regular anovulatory cycles, it is usually started on the 5th day after the onset of menstruation. It must be realised that the response to clomiphene is unpredictable and the dosage effective in one patient may prove inadequate in others. Following clomiphene, ovulation can occur in about 70% of women; of these less than 50% may conceive.

The drug, however, has similar drawbacks as HPG-HCG combination therapy. The multiple pregnancy rate of 6% is distinctly lower than that with gonadotropin therapy (20%), but the pregnancy wastage rate (20%) is similar with both therapies. As compared to human pituitary gonadotropin, clomiphene is a less effective but a less hazardous drug. It is claimed that the incidence of abortions can be reduced by using progesterone soon after the existence of conception is confirmed.

(2) Clomiphene has also been used in males with low sperm counts with variable results. The dose used is 50 mg. daily

for three months since sperm maturation takes 69-72 days. With these doses, the sperm count often rises. Larger doses than this, however, actually suppress spermatogenesis.

(3) It can also be used to regulate the menses in a patient with anovulatory cycles associated with irregular periods.

CYCLOFENIL (Ondomid): This compound has a structure similar to clomiphene and is used for similar purposes. It is available as 100 mg. tablets. It does not exert a peripheral anti-estrogenic effect. Given in the dose of 500-800 mg. per day for 5-10 days, cyclically, it induces ovulation.

63 Androgens and Anabolic Steroids

Most of the early knowledge regarding the relationship between the testes and the secondary sex characters in male was obtained from the studies in castrated animals. It was demonstrated that the typical signs of castration could be reversed by transplantation of gonads. The first pure hormone with androgenic activity—*androsterone*—was isolated from the male urine by Butenandt in 1931. This was followed by the isolation of another urinary androgenic steroid, *dehydroepiandrosterone*. The active principle of testes is a steroid *testosterone*, isolated in pure form in 1935; the urinary products like androsterone and etiocholanolone are the metabolic products of testosterone. Steroidogenesis also occurs in the ovary, the adrenal cortical tissue and the placenta.

Physiological actions of androgens: Androgens determine the differentiation of the foetal external genitals in the male direction. Further, in males they prevent the development of the hypothalamic function responsible for the cyclic release of LH. At puberty, testosterone secretion increases markedly and is responsible for transforming a boy into man. The increase in gonadotropin secretion at puberty is attributed to a reduction in the sensitivity of the hypothalamus to the circulating androgens. Following this increase, testes enlarge and the testicular activity is initiated. FSH is responsible for the growth of the testes and acts mainly on the seminiferous tubules which produce spermatozoa. It promotes spermatogenesis and stimulates the metabolic activity of the Sertoli cells. It is thus gametogenic in action. LH (ICSH) stimulates the development and differentiation of the leydig cells at puberty, leading to a marked rise in plasma testosterone which is essential for spermatogenesis, maturation of the sperms and the development of secondary sex characters in male. Thus, both FSH and LH play an important role in initiating and maintaining the normal testicular functions. These are:

(a) Development of male sex organs like penis, scrotum, and secondary sex characters like pubic hair, beard and change in voice.

(b) Development of the seminal vesicles, prostate and epididymis.

(c) Maintenance of spermatogenesis.

(d) Development of skeletal musculature and emotional get up of male type.

(e) Anabolic and growth promoting effect.

Failure of the testicular function causes male hypogonadism.

The daily testosterone production by male adults is estimated to be between 4 to 12 mg. This gives a plasma level between 400 to 1000 ng. per cent. A small proportion of the circulating testosterone may arise directly from the adrenal cortex or indirectly in the liver and kidneys from the metabolism of weaker androgens; this is of little significance in the male. In the female, the latter is the only source of plasma testosterone which measures 20 to 40 ng. per cent. The hormone is converted by androgen responsive tissues to the highly active metabolite, *dihydrotestosterone*, which is believed to be the active form of the hormone. Dihydrotestosterone binds to a cytoplasmic protein receptor before acting on the nucleus. The lack of this protein receptor is believed to result in the syndrome of testicular feminization with complete androgen insensitivity. About 0.5

per cent of testosterone is converted to estrogens in the body.

Male hypogonadism: Testicular function can be affected either by primary failure of the testes or secondarily by failure of the anterior pituitary hypothalamic complex. In case of primary testicular failure, gonadotropin secretion is increased, producing *hypergonadotropic hypogonadism*, while in case of pituitary-hypothalamic failure, the gonadotropin secretion is decreased, causing *hypogonadotropic hypogonadism*.

The testicular deficiency could be selectively gametogenic or both gameto- and androgenic. In the former the individual is sterile but has normal secondary sex characters; in the second case both the functions are affected.

Failure of the testes before puberty causes infantile penis, feminine distribution of fat (more on buttocks, breast and hips) and arrest of laryngeal and hair growth. The muscles become soft, skin becomes smooth and there is a lack of sexual drive. Intelligence is not affected.

In a patient with post-puberal hypogonadism, the general body proportions and size of the penis are not affected. But the body hair become sparse and silky, voice becomes high pitched and libido is greatly reduced. Skeletal muscles become flabby and weak and there is a tendency to develop obesity. However, normal life expectancy is not shortened nor is premature senility produced. The volume of semen is markedly decreased and there is a change in the emotional get up, anxiety, fear and inferiority complex replacing the original confidence and vigour.

Pharmacological actions of androgens:

(a) **Androgenic action:** Administration of testosterone in prepuberal castrated individuals reverses most of the changes seen in hypogonadism. The secondary sex characteristics develop, muscle strength is increased and sexual desire and erections occur normally.

Androgen is shown to maintain spermatogenesis in hypophysectomised rats but this is doubtful in man.

Given to females, testosterone causes masculinization, e.g. hirsutism, growth of clitoris and change in voice (male type). It also alters the ovarian function. Thus, the development of proliferative phase of the endometrium may be inhibited and large doses can suppress the ovulation and lactation. Administered during pregnancy, androgenic compounds can exert masculinizing effect on developing female foetus.

(b) **Anabolic actions:** Protein synthesis (anabolism) and protein breakdown (catabolism) are the important functions of a cell. Adequate supply of nutrient material is necessary for protein synthesis. These anabolic or catabolic functions can be modified by various factors including hormones. The anabolic action of androgens is demonstrated by the fact that the male is more muscular than the female and that castration in male causes reduction in muscle mass, which can be prevented by replacement therapy with testosterone. Since anabolism involves protein synthesis, biochemically it can be demonstrated by measuring nitrogen retention. Testosterone promotes nitrogen retention and increases the muscle mass and body weight in castrated individuals of both sexes. Along with nitrogen, potassium, sulfur and phosphorous are also retained, while the urinary excretion of calcium and creatinine is decreased. The anabolic action is marked in eunuchoid men, in prepuberal boys and in women. It is insignificant in normal healthy males. The effect is specific and can be observed with small doses of testosterone which do not produce significant androgenic effects.

Androgens, given in smaller doses, can promote growth of epiphyseal cartilage, particularly in dwarfism due to hypopituitarism and hypogonadism. However, in large doses testosterone will thwart the final height reached by bringing about early fusion of the epiphyses.

Androgens may reduce bone resorption and cause beneficial effects in senile osteoporosis. No such effect is, however, observed in idiopathic osteoporosis in young patients where sex hormone deficiency is not present.

(c) **Effect on pituitary:** The nature of the control of pituitary gonadotropin secretion by testosterone is not very clear. Administration of LH increases the plasma level of testosterone while some synthetic androgens inhibit LH secretion resulting into decrease in plasma testosterone. Such feed back effect has not been observed in the production of FSH in man. The LH inhibiting action could be due to the small quantities of estrogen to which testosterone is converted in the body, as mesterolone, a new testosterone analogue, which is not converted into estrogen, lacks this gonadotropin inhibiting property.

(d) **Miscellaneous actions:** Androgens have been shown to increase appetite and cause a feeling of well being. The mechanism of this action is not known, but it is not observed in adult male with normal gonadal function.

Androgens can cause sodium retention and edema, probably by their action on renal tubules. Androgens also cause growth and increased secretion of the sebaceous glands, clinically manifested as acne. These compounds generally antagonize many of the actions of estrogens in females. They stimulate erythropoietin secretion by the kidneys and directly stimulate heme synthesis in the bone marrow as well. These actions probably account for the differences in hemoglobin levels between men and women and are of importance in the treatment of certain anemias with testosterone.

Absorption, fate and excretion: Testosterone is well absorbed when given orally but is largely inactivated by the liver and hence, is therapeutically ineffective. Its 17 methyl derivatives methyl-testosterone and fluoxymesterone are much less destroyed by the liver and are effective orally.

Ninety-eight per cent of plasma testosterone is protein bound and only two per cent is free. Its plasma half-life is about 10-20 minutes. About 90% of testosterone is metabolised in the body, mainly in the liver, and excreted in the urine, mostly as androsterone and its isomer etiocholanolone, as sulfates and glucuronides. Although these excretory products can be measured as 17-ketosteroids in the urine, such measurement does not necessarily give a correct idea of testicular activity as the major urinary fraction of 17-ketosteroids comes from the metabolism of adrenal androgens. The plasma testosterone levels are a useful indicator of androgen production in the male.

Like estrogens, esters of testosterone with weak organic acids like propionic acid, when injected produce prolonged action for 2-3 days, while cypionate and enanthate are effective for 1-2 weeks. Pellets of testosterone implanted under the skin are slowly absorbed and their therapeutic action lasts for 6-8 months.

Bioassay of androgenic action: Androgens used therapeutically are pure substances and hence, do not need bioassay. The androgenic activity of a new compound is assayed by observing the growth of a capon comb or comb of a newly hatced chick. The other method involves the measurement of growth of the seminal vesicles, or the prostate in castrated rats. Clinical androgenicity of different compounds correlates better with the results of the latter group of assays.

Preparations and dosage:

(1) *Testosterone* aqueous suspension (Aquaviron) 25 mg/ml. Dose, 50-100 mg. once a fortnight. The aqueous suspension has a moderately prolonged action.

(2) *Testosterone esters*:

(a) Testosterone propionate injection I.P. (in ethyl oleate) Dose, 5-25 mg. I.M. every 1-3 days.

(b) Testosterone phenylpropionate 50-100 mg. I.M. every 7-14 days.

(c) Testosterone cypionate, 50-100 mg. I.M. every 7-14 days.

(d) Testosterone enanthate, 200 mg. I.M. every 2-4 weeks.

(3) *Orally active preparations:* These

are 17- or 1-methylated testosterone derivatives.

(a) Methyl testosterone tablet I.P contains 5 mg. of the drug. Dose: 25 to 50 mg. daily in male; 5 to 20 mg. daily for a female. In the treatment of mammary carcinoma, 50 to 100 mg. daily.

(b) Fluoxymesterone B.P. (Ultandren): Available as 5 mg. tablets. Dose: 5 to 10 mg. daily in hypogonadism, 20 mg. daily in inoperable breast cancer and 1 to 5 mg. daily in the treatment of functional uterine bleeding and dysmenorrhea.

(c) Mesterolone: Available as 25 mg. tablets. Dose 25—100 mg daily. It is not hepatotoxic nor is it converted to estrogen in the body. It owes these properties to its methyl group at C_1 instead of at C_{17} as in methyltestosterone and fluoxymesterone.

Adverse reactions:

(a) Androgens in large doses can cause enlargement of clitoris, deepening of voice, baldness, hirsutism, acne and masculinization in females and precocious puberty in males. Some of these changes are irreversible.

(b) In young children, prolonged use of these drugs in large doses may bring about early closure of the epiphyses and thus stop the growth.

(c) Large doses given in adult males can suppress spermatogenesis and may even cause degeneration of seminiferous tubules.

(d) Large doses can cause retention of sodium and edema. This can be corrected by giving diuretics.

(e) Methyl testosterone, fluoxymesterone and many anabolic steroids are potentially hepatotoxic and can give rise to cholestatic type of jaundice.

(f) Hepatic adenocarcinoma has been reported in a few patients of aplastic anemia receiving 17-alkyl derivatives for prolonged periods (1-7 years).

Therapeutic uses of testosterone: This drug can be used either for its androgenic and antiestrogenic actions or for its anabolic effects. The important uses are:

For replacement therapy ✓

(1) **Hypogonadism:** In primary testicular failure the treatment should be started at the time of puberty. Long acting preparation of testosterone is generally used in the dose of 200 mg. every 1-2 weeks for 2-3 years and then maintained by a single injection every month. Other preparations can also be used but more frequent administration is necessary. Oral preparations are not very effective in initiating sexual development but are often adequate for maintenance therapy.

It must be emphasized that the diagnosis of hypogonadism in young children should be made cautiously because of marked variations in age of maturation in different individuals. Testosterone should not be used simply to hasten the changes of puberty and sexual maturation in otherwise normal boys.

In post-puberal hypogonadism only replacement therapy is needed and long acting testosterone preparation is given in the dose of 200 mg. every month. Alternatively, oral testosterone esters may be used daily.

In hypopituitarism in children shortage of HGH makes it necessary to use an androgen. Hydrocortisone and thyroxine may be added if necessary. ✓

(2) **Male 'climacteric':** Although there is no such clear-cut condition parallel to 'female climacteric' in elderly males, testicular function is reduced as the age advances. This is manifested as muscular weakness and tendency to obesity. In such cases small doses of testosterone may be useful. It must be realized, however, that the criteria for the diagnosis of such condition are very vague.

For pharmacological therapy: ✓

(1) **Senile osteoporosis:** Both estrogen and testosterone may be useful in the treatment of senile osteoporosis, provided the dietetic intake of calcium is adequate. ✓

(2) **Carcinoma of the breast** in premenopausal female: This is discussed in Chapter 55. ✓

(3) **As anabolic steroid:** To promote

anabolism. This is discussed in detail below.

(4) **Impotence:** Impotence may be defined as an inability for a man to have satisfactory sexual intercourse. This could be due to lack of desire, inability to attain or maintain adequate penile erection, or premature ejaculation. In the majority of patients, impotence is usually psychosexual and simple sex education and behaviour therapy is all that is necessary; mental depression, anxiety and social problems, if present, need attention. Unfortunately, a variety of remedies (many of them expensive) of dubious value are promoted for the treatment of impotence. Occasionally, nonendocrine causes such as chronic liver disease, diabetes mellitus, urethritis and prostatitis may be present. Only rarely is a hormonal disturbance the cause of the symptom where endocrine treatment is indicated. In such cases, long acting testosterone esters in the dose of 100-250 mg every two to four weeks may be useful; it should be noted that the older patients are more prone to the undesirable adverse effects of these drugs.

Finally, it is important to enquire from the patient whether he is taking any drugs such as alcohol, opiates, antihypertensive agents, barbiturates, benzodiazepines, antipsychotics, antiandrogens, estrogens, corticosteroids, antihistamines and spironolactone, all of which are known to cause loss of libido, erection or ejaculation.

(5) **Miscellaneous conditions:** Androgens in large doses are useful in refractory anemias, particularly aplastic anemia and anemia of chronic renal failure. Testosterone can be used effectively for suppressing lactation; 50-100 mg of testosterone propionate may be injected daily for 4 days, beginning on the day of delivery.

Its use in menstrual disorders is now made obsolete by the availability of synthetic progestins and combination oral contraceptives.

Androgens are absolutely contraindicated in carcinoma of prostate and breast in males.

ANABOLIC STEROIDS

Although testosterone has potent anabolic activity it cannot be used freely for this property because of its equally potent androgenic action. Hence, various steroids have been synthesized with anabolic actions but reduced virilizing effects. The clinically used anabolic steroids are given in Table 63.1. With the exception of methenolone and nandrolone, they are all C_{17} alkyl substituted steroids. None of the presently available compounds, however, is selectively anabolic, without any androgenic action.

Chemically, these drugs are derivatives of testosterone or methyl testosterone.

Bioassay of anabolic action: This is usually based on the measurement of growth of levator ani muscle (anabolic activity) of the castrated rat as compared to the growth of the prostate and seminal vesicles (androgenic activity) in the same animal. The ratio of anabolic to androgenic activity is calculated and compared with that in control animals given testosterone; testosterone is considered to have an anabolic to androgenic ratio of one. Therapeutically useful anabolic steroids should have this ratio greater than 2. These assays, however, are not very precise and give variable results in different laboratories. The choice of levator ani for this test was probably unfortunate because it is an intimate part of the genital apparatus and its response to androgens is not shared by other skeletal muscles.

Pharmacological actions: In therapeutic doses the anabolic action is predominant. The androgenic effect becomes more and more apparent as the therapy is prolonged, particularly in females. Some individuals appear to be very sensitive to the androgenic effects of these compounds; unfortunately, this cannot be predicted. Androgenic properties are similar to those of testosterone.

(a) **Protein anabolism:** Anabolic steroids promote protein anabolism. Clinically, this is manifested by increase in the muscle mass and the body weight. Factors controlling the protein synthesis by the cell are not well understood. Protein catabolism or negative nitrogen balance is observed in various disease states such as caloric deficiency, protein deficiency, fever, infections, all forms of stress, prolonged immobilization and following broad spectrum antibiotics. Tissues like liver and muscle lose proteins more quickly than others like brain. In majority of these conditions simply correction of the cause and providing adequate calories and nutrients including proteins will accelerate the anabolism. Anabolic steroids are certainly not effective during the acute phase of the illness or continuing stress. Used during recovery from such conditions, they may promote positive nitrogen balance but the therapeutic implication of this effect is not definite.

It must be emphasized that protein synthesis and tissue repair are natural phenomena following tissue injury. For this, what is usually needed is enough amount of protein intake in the diet; the necessary anabolic drive is provided by the body. Various studies have stressed that there is no lack of anabolic drive both in men and women recovering from illness; and the necessity of anabolic steroids in such conditions to provide the anabolic drive is highly questionable.

(b) **Anticatabolic effects:** In short term studies, anabolic steroids have been shown to produce positive nitrogen balance in individuals on prolonged glucocorticoid therapy. It is believed, therefore, that anabolic steroids counter the catabolic effects of glucocorticoids. Glucocorticoids do cause protein depletion as seen in Cushing's disease. However, the catabolic changes seen in Cushing's disease have no similarity to other wasting illnesses. Though glucocorticoids cause depletion of proteins from muscles, they increase liver proteins; further, there is an increased synthesis of glycogen and fat. The main site of action of glucocorticoids is the liver. The anabolic steroids, however, accelerate the protein synthesis in all cells. It is not clear, therefore, whether nitrogen retention following anabolic steroids has any protective action against catabolic processes due to glucocorticoids. They may, however, be beneficial because of their nonspecific action of improving appetite and producing a feeling of well being.

Use of anabolic steroids routinely with glucocorticoids may be dangerous as certain adverse effects due to glucocorticoids such as hypertension, acne, hirsutism and sodium retention may be increased by anabolic steroids.

(c) **Progestational effects:** Some of the anabolic steroids like norethandrolone have significant progestational activity.

(d) **Miscellaneous actions:** Like testosterone anabolic steroids may reduce bone resorption and thus may prevent osteoporosis in certain cases.

Adverse reactions: These are due to their androgenic action and are similar to those produced by testosterone. The use of anabolic steroids in pregnancy has led to virilization of the foetus and even if no external evidence of this is apparent at birth some infants have shown an advanced bone age which could adversely affect future growth. In addition, the orally active anabolic steroids which have a substituted alkyl group at C_{17} are potentially hepatotoxic; these drugs can cause cholestatic jaundice and death due to liver damage has been reported. The hepatotoxicity is probably dose dependent. Prolonged treatment with anabolic steroids may lead to sodium and water retention. Norethandrolone sometimes causes impotence in the male because of gonadotropin suppression.

Preparations and dosage: Various commercially available anabolic steroids are given in the Table 63.1. The pediatric doses of these drugs are: methandienone 0.04 mg./kg./day; ethylestrenol 0.1-0.2 mg./kg./day; oxandrolone 0.1 mg./kg./day. Methyl-testosterone may also be

Table 63.1: **Anabolic Steroids**

Generic name (Trade name)	Recommended adult dose
Nandrolone Phenyl propionate* (Durabolin)	25-50 mg. every week
Nandrolone decanoate* (Deca-Durabolin)	25-50 mg. every three weeks
Methenolone acetate (Primobolan)	10-20 mg. daily
Oxymetholone (Adroyd)	5-15 mg. daily
Methandienone (Dianabol)	2.5-15 mg. daily
Ethylestrenol (Orabolin)	2-4 mg. daily
Norethandrolone (Nilevar)	20-30 mg. daily
Oxandrolone (Anavar)	15-30 mg. daily
Oxymesterone (Oranabol)	10-40 mg. daily

*These are given I.M.; the rest are given orally. The first three are derivatives of testosterone; the rest of methyl-testosterone.

used for the same purpose in children in the total daily dose of 5 mg or less.

Therapeutic uses:

(1) They may be used during chronic illnesses to accelerate rebuilding of tissues. It must be emphasized that anabolic steroids are not a substitute for adequate protein intake and their use in treatment of such conditions as protein malnutrition, without ensuring adequate diet, is wasteful. It is difficult to substantiate the superiority of one preparation over the others and for short term therapy in children and females and long term therapy in males, testosterone itself may be as good as other costly compounds.

(2) They are sometimes useful in postmenopausal and senile osteoporosis.

(3) They are used to promote growth in hypogonadal children and pituitary dwarfs. Excessive dosage in such cases can cause premature fusion of the epiphyses. Their place in the treatment of retarded children is very limited.

(4) They are sometimes used in acute or chronic renal failure, along with protein restriction, to reduce blood urea and thus to decrease the nitrogen load on the kidneys.

(5) In carcinoma of the breast in females.

(6) They are claimed to be effective in certain refractory anemias associated with bone marrow hypoplasia or aplasia.

Anabolic steroids are contraindicated in prostatic and male breast cancer; they should be used cautiously in the presence of cardiac, renal and hepatic diseases and during pregnancy.

Causes of failure to gain weight by apparently healthy individuals are many times undetectable. Use of anabolic steroids to increase the body weight in such thin but otherwise healthy children or adults is disappointing; even some of those who appear to benefit, lose the weight as soon as the drug is stopped. Anabolic steroids are not tonics and should not be used to treat nonspecific symptoms like anorexia and loss of weight without investigating the cause. They are useless in the absence of adequate protein intake and prescribing of such costly medication for a patient who cannot afford even a proper diet is totally unjustified. Unfortunately, anabolic steroids like tranquillisers are presently more misused than used.

ANTIANDROGENS

Any compound which antagonizes or interferes with the action of androgens is referred to as an antiandrogen. Estrogens and certain progestins exert such antiandrogenic action at the tissue level; further, they suppress the pituitary gonadotropin release.

CYPROTERONE ACETATE: This drug has an antiandrogenic and some progestogenic action. Its antiandrogenic action is due to interference with the binding of dihydrotestosterone to receptors in the nuclei of the target cells. By its progestogenic effect, it reduces the plasma level of gonadotropin and testosterone. Cyproterone, unlike cyproterone acetate, exerts only the peripheral antiandrogenic action. Cyproterone acetate is used orally in the dose of 50-100 mg. per day to reduce libido and sexual potency in deviant hypersexuality in males. It has been used with some success in precocious puberty in boys, in female hirsutism and in carcinoma of the prostate.

64 Calcium, Phosphorus, Magnesium and Fluoride Metabolism, Parathyroid and Vitamin D

Calcium, apart from forming an essential constituent of bones, plays an important role in body homeostasis and disturbances in calcium metabolism are associated with derangement of various cellular functions. In most areas, food is the only important source of calcium. Milk and milk products are an excellent source of completely assimilable calcium; green leafy vegetables and cereals are rich in calcium but their calcium is relatively less well utilized because of the concurrent presence of oxalates and phytates, respectively. Ragi is especially rich and rice (especially highly polished one) very poor in calcium content. The habit of chewing pan with slaked lime applied to it contributes to the intake of calcium in Indians. In certain areas, drinking water contains calcium salts and contributes to the calcium intake.

The optimum calcium intake for humans is not known. It is estimated to be 500-600 mg./day in infants and adults and 600-700 mg. in growing children. Mature foetus contains about 30 g. of calcium which constitutes 3-4 per cent of the total calcium in the mother. Most of it is deposited during the last trimester of pregnancy; loss of maternal calcium during lactation is still more, which needs correction by adding 1 g. of calcium supplement daily. One year old baby contains about 100 g. of calcium, a gain of 70 g. over the total calcium content at birth—most of which is supplied from the milk. Calcium requirement is also higher in those who, for any reason, lose excessive amounts of calcium in the urine.

The average daily diet of Indians, which is based mainly on milled rice and very little of milk, may contain as little as 0.2 g. of calcium.

Body distribution: An adult human body weighing 70 kg. contains about 1.2 to 1.4 kg. of calcium. Ninety-nine per cent of the body calcium is present in bones.

The bone mineral exists in the form of a complex salt containing calcium, phosphate and carbonate. The bone is not an idle store of minerals but is constantly contributing to the maintenance of extracellular levels of calcium and phosphorus. It does so by two processes: (a) a simple process of exchange between the newly deposited bone mineral and the extracellular ionic calcium; and (b) a process of constant and concurrent formation and resorption of bone, controlled by parathyroid hormone, calcitonin and vitamin D. This latter process affects the older deposited bone mineral but not the freshly deposited one.

Blood calcium: Calcium is essentially distributed extracellularly, its concentration being maintained within narrow limits by deposition or release from the bone, renal tubular reabsorption and intestinal absorption. Most of the calcium in the blood is present in the plasma; R.B.Cs. contain little calcium. The human plasma contains 9 to 11 mg. of calcium per 100 ml. The plasma calcium is present as (i) ionized, (ii) protein bound and (iii) combined with citrate and other organic acids, the normal plasma ionized calcium being about 65 per cent of the total.

The protein bound fraction is not ultrafilterable, physiologically inactive and is not filtered in the glomeruli. The rest of the plasma calcium is ultra-filterable. Of this, the ionic fraction is diffusible, physiologically active and is the portion which exchanges with the bone calcium; it is also the portion which is affected by bone formation and resorption and which regulates the rates of secretion of the parathyroid hormone and calcitonin. Plasma level of ionic calcium is about 5.9—6.5 mg./100 ml.

Calcium content of other tissues is relatively small.

Absorption of calcium: Calcium is mainly absorbed from the jejunum and partly from the ileum. The absorption is partly by passive diffusion and partly by an active process. It has been postulated that calcium binding to a carrier protein in the cells of the villi regulates its rate of absorption.

Absorption of calcium is at best partial. Calcium secreted in the gestrointestinal juices is added to the dietary calcium and the net calcium absorption on a daily diet containing 1 g. of calcium is about 200-300 mg. per day. However, as an adaptive mechanism, even in the presence of daily calcium intake of less than 1 g., absorption of calcium remains within normal limits provided the supply of vitamin D is adequate.

Absorption of calcium is stimulated physiologically by the parathyroid hormone, vitamin D, an acid residue in the intestines and a high protein diet. It is also stimulated by the presence of a negative calcium balance i.e. calcium deficiency.

Calcium absorption is defective in the presence of deficiencies of parathyroid hormone and/or vitamin D and is interfered with by an excess of phosphates, oxalates (from vegetables) or phytate (from cereals) and excess fatty acids (in patients with steatorrhoea). Fat intake, however, does not interfere with calcium absorption in normal subjects. Human milk contains proportionately less phosphorus (Ca:P-2.2:1) than cow's milk which has a Ca : P ratio of 1.1:1. Hence, in infants the calcium absorption from human milk is more efficient than from cow's milk. Mean calcium content of cow's milk, however, is 125 mg. per cent as against 33 mg. per cent in human milk. Corticosteroids also reduce intestinal absorption of calcium.

Excretion of calcium: Calcium is excreted in feces, urine and sweat. The total amount of calcium secreted in the intestinal tract is about 200 mg. daily, of which 130 mg. is excreted in feces. Decreased dietetic calcium intake (as in starvation) and lack of vitamin D will thus cause marked deficiency of calcium as the fecal loss is not affected.

Ninety-seven per cent of the calcium filtered by the kidney is reabsorbed by the tubules under the influence of the parathyroid hormone and vitamin D. Calcitonin inhibits proximal tubular reabsorption of calcium and increases its urinary excretion. There is no tubular secretion of calcium. The urine contains 2 to 6 mg. of calcium per kg. body weight per 24 hours; it is 155 mg. daily in Indians who consume milk as compared to 80 mg. in those whose calcium intake is low. A rise in plasma ionic calcium from any cause (hyperparathyroidism, hypervitaminosis D, excessive bone resorption or bone destruction) presents a larger load of calcium to the tubules leading to increased urinary excretion of calcium; however, it rarely exceeds 500 mg. per day.

The reasons for failure of calcium to precipitate in normal urine are not known. If the urine becomes alkaline it is precipitated as calcium phosphate. Recently two peptides have been isolated from urine and plasma, claimed to be potent inhibitors of calcium crystallization.

Urinary excretion of calcium increases in hypercalcemia from any cause (including hyperparathyroidism), metabolic acidosis, hyperthyroidism, acromegaly, hypercorticism, in urinary tract infections and following a high intake of magnesium. It is reduced in hypoparathyroidism, renal failure and in metabolic alkalosis. For physiological reasons, it is reduced in hypocalcemic states.

Excretion of calcium in the sweat is

negligible in the temperate climate but may be significant in the tropics because of the large volume of sweat secreted.

Physiological functions:

(1) *Excitability:* Calcium is an important component of the cell membrane and controls its permeability and electrical properties. Calcium ions compete with sodium ions for sites on the membrane. An excess of extracellular calcium reduces the permeability of the membrane to sodium and thus raises the critical level of depolarization at which sodium permeability is increased and the action potential fired off. This stabilizes the membrane and reduces its excitability. Thus, it is well known that hypercalcemia reduces the excitability of nerves and muscles. Hypocalcemia acts in exactly the opposite manner by increasing membrane permeability to sodium and thus reducing its excitation threshold close to the resting membrane potential. However, concurrent hypokalemia and/or acidosis protects against hypocalcemic tetany.

(2) *Coupling between excitation and response* (Second messenger): Calcium is essential as a coupling factor between excitation and contraction in all forms of muscle and between stimulus and secretion in certain endocrine glands e.g. release of ADH by nerve impulses to the neurohypophysis and of catecholamines from the adrenal medulla by acetylcholine. In mediating these responses, calcium is presumably released from the cell membrane into the cell to activate the contractile processes or cause release of stored hormone from the granules. Further, certain drugs acting on the heart are believed to owe their action to promotion (digitalis) or inhibition (verapamil) of entry of calcium ions into the cells.

(3) *Formation of bone and teeth*: Calcium is essential for proper formation of bone and teeth and calcium deficiency during intra-uterine life and during the extra-uterine growth period leads to delayed and defective dentition and poor bone formation.

A negative calcium balance leads to *osteoporosis*, a bone disorder in which the bones are chemically normal in composition but in which the total bone mass is reduced.

By itself, a negative calcium balance (i.e. calcium deficiency) does not give rise to *osteomalacia*, a disorder in which the mineral content of the bone is reduced and bone shows an abnormal chemical composition. Osteomalacia is a manifestation of vitamin D deficiency, defective vitamin D metabolism or of resistance to the action of vitamin D. Alternatively, it is a manifestation of excessive phosphate deficiency.

(4) *Coagulation of blood*: Plasma ionic calcium is essential for the conversion of prothrombin to thrombin.

(5) *Renal concentrating mechanisms*: Ability to concentrate the urine maximally is impaired in hypercalcemia and in hypokalemia.

Pharmacological actions of calcium: Pharmacological actions of calcium ions are best illustrated by a description of the effects of hyper and hypocalcemic states.

Hypercalcemia: Hypercalcemia occurs in primary hyperparathyroidism, tertiary hyperparathyroidism (a condition in which one of the hyperplastic parathyroid glands in a patient with chronic renal failure becomes adenomatous and autonomous), hypervitaminosis D, excessive bone destruction by metastases or by myelomatosis and bronchogenic carcinoma (even in the absence of bony metastases).

The effects of hypercalcemia are felt far and wide. They are characterised by lethargy, anorexia, weakness, muscular hypotonia, nausea, vomiting and severe constipation. Kidneys show inability to concentrate the urine and polyuria and dehydration may occur. Heart may show irregularities. Excess calcium gets deposited in various tissues (metastatic calcification) such as arteries, cornea, muscles and kidneys. The development of mental changes indicates severe hypercalcemia (over 15 mg.%) and is a medical emergency.

Hypocalcemia: Hypocalcemia occurs in

vitamin D deficiency states, vitamin D resistant states, hypoparathyroidism and in renal failure. It is characterised by increased neuromuscular irritability with paraesthesiae, tetany, convulsions and laryngeal spasm. Teeth that develop subsequent to the onset of disease show hypoplasia. Skin and nails may show atrophy. These effects of hypocalcemia are essentially reversible on restoration of the normocalcemic state.

Adverse reactions: Orally administered calcium salts produce constipation and rarely intestinal obstruction due to formation of calcium concretions. Calcium chloride solution is irritating by all routes. Extravasation of calcium salts during intravenous administration may lead to local sloughing. Intravenous administration of calcium in digitalized patients can cause cardiac arrhythmias and cardiac arrest. Oral calcium does not cause hypercalcemia except in Milk Alkali Syndrome and rarely in hypothyroidism.

Preparations and dosage: These are given in Table 64.1.

Table 64.1

Calcium Content of Various Calcium Salts

Calcium Salts	Ca content mg. per G. of salt	Grams required to provide 1 G. of Ca
Carbonate	400	2.5
Chloride	360	2.8
Phosphate	230	4.4
Citrate	211	4.7
Glycerophosphate	162	6.2
Lactate	130	7.7
Gluconate	89	11
Heptagluconate	82	12
Calcium Sandoz	63	16

Reproduced from Fourman P., Calcium Supplements, Prescribers' Journal, 6, 25, 1966.

Of the preparations available for oral therapy, calcium lactate has a sour taste and is sparingly soluble in water. Calcium gluconate is also poorly soluble but can be made soluble by the addition of a stabilizer. Calcium citrate is tasteless and water soluble. All calcium compounds are poorly absorbed. Calcium carbonate, however, is cheap, tasteless and as effective as the other salts and should therefore, be preferred.

Calcium compounds available for parenteral therapy are:

(1) Calcium chloride hydrate I.P. is an ingredient of compound sodium lactate injection and compound sodium chloride injection. Dose: 0.6 to 2 g. through I.V. drip.

(ii) Calcium gluconate injection I.P. contains 1 g. of the salt in 10 ml. Dose: 1 to 2 g. (10 to 20 ml of 10% solution) I.V.

(iii) Calcium laevulinate injection: given I.M. or I.V. as a 10% solution. Its calcium content is 13%.

Therapeutic uses of calcium salts:

(1) To prevent or correct calcium deficiency, oral supplements of calcium are used. This is necessary:

(a) in growing children, pregnant women and lactating mothers,

(b) in individuals with diets deficient in calcium.

(c) in patients with post-menopausal osteoporosis and osteoporosis due to Cushing's syndrome,

(d) in patients on long term corticosteroid therapy,

(e) in individual with excessive urinary loss of calcium,

(f) in patients with vitamin D deficiency rickets and osteomalacia, who are put on vitamin D therapy, and

(g) for prolonged periods after removal of a parathyroid tumour, especially in patients with extensive bone involvement.

(2) Calcium carbonate is used as an antacid.

(3) Calcium gluconate or chloride is used intravenously in the acute treatment of tetany and lead colic and to counter the systemic effects of magnesium salts and hypocalcemia. Intravenous infusions of calcium are useful in alleviating bone pains

and in promoting bone healing in patients with renal failure who develop secondary hyperparathyroidism.

(4) Calcium forms an important constituent of 'physiological solutions', such as Darrow's or Hartman's for infusion.

(5) Calcium salts are sometimes used for treating urticaria and nonspecific intestinal colic with variable results. An intravenous injection of calcium gluconate is one of the commonest placebos used in general practices and produces a feeling of warmth which spreads as a wave all over the body.

Treatment of hypercalcemia: This comprises the treatment of the cause, reduction of dietary intake of calcium and the administration of sodium phytate (9 g. per day) orally to bind calcium in the gut. Glucocorticoids are helpful in reducing the plasma calcium level in patients with metastatic bone disease. When the plasma calcium is over 15 mg., it is a medical emergency (hypercalcemic crisis). The treatment of hypercalcemic crisis consists of (1) correction of dehydration and induction of a solute (NaCl) diuresis by using isotonic saline infusion liberally and furosemide. This increases the urinary loss of calcium. Thiazides should not be used for this purpose as they cause calcium retention by the kidneys; (2) neutral inorganic phosphate solution given intravenously (see later); (3) glucocorticoids are used in large doses (prednisolone 20-30 mg. every 12 hours) but take 1-2 weeks to act and cannot be relied upon by themselves unlike in chronic hypercalcemia; (4) mithramycin (Chapter 55); (5) potassium is useful to counter the action of calcium on the heart especially if there is concurrent hypokalemia.

PHOSPHORUS METABOLISM

Phosphorus is abundantly present in almost all foods; milk, meat, fish, cereals, pulses and nuts are rich in phosphorus. A part of the phosphorus in cereals is present as phytate and is unassimilable. Phosphorus deficiency is rarely encountered in India because the diets of even the poorer sections of the population are composed mainly of cereals which are rich in phosphorus.

Dietary requirements: Daily requirement of phosphorus is estimated at about 0.9 g. in adults. It is higher in growing children, pregnant women and lactating mothers.

Body distribution: The total phosphorus content of the average adult human body is about 500-600 g. 75 per cent of which is present in bones and 25 per cent in other tissues.

The red blood cells contain far more phosphorus than the plasma; hence, even slight hemolysis gives fallaciously high plasma phosphorus values. The plasma phosphorus is present in three forms: inorganic phosphorus (3 to 5 mg. per cent), ester phosphorus (0.1 to 1.7 mg. per cent) and lipid phosphorus (7 to 15 mg. per cent). The term 'plasma phosphate' usually means the plasma inorganic phosphate measured as phosphorus. The plasma inorganic phosphorus concentration varies with age, dietary intake of phosphorus and in relation to meals. It is intimately related to carbohydrate metabolism and falls significantly during glucose utilization. Phosphorus present in other tissues is present in the form of nucleoproteins. Vitamin D stimulates the intestinal absorption of calcium and of phosphorus.

Absorption and excretion: Absorption of phosphorus is more complete than that of calcium. About 70 per cent of the dietary phosphorus is absorbed in the small bowel. A high calcium intake and aluminium hydroxide in large doses interfere with its absorption. Phosphorus filtered by glomeruli is largely reabsorbed by tubules and some is secreted by cells of the distal tubules. The urinary excretion of phosphorus is under the control of the parathyroid hormone which diminishes its tubular reabsorption and hence, increases its excretion. The excretion also increases with increasing levels of plasma inorganic phosphorus. Urinary excretion of phosphorus is more intimately related to its dietary intake than is the case with calcium.

Physiological functions:

(1) *Formation of bone and teeth:* Along with calcium, phosphorus is essential for the formation of healthy bones and teeth. Phosphorus needed for this purpose is made available 'on site' by the action of alkaline phosphatase on organic phosphates. When the ion product, Ca x P, exceeds a critical level locally, deposition of calcium phosphate as crystals commences.

(2) *Phosphorylation:* Phosphorylation includes all chemical reactions involving combination with phosphoric acid. Phosphorylation is an essential step in the metabolism of almost all endogenous substances in the body.

(3) *Miscellaneous:* Phosphorus forms an integral part of the structure of the nuclei and cytoplasm. Further, energy is stored in the form of 'high energy phosphate bonds.' Phosphates also play an important role in the regulation of the hydrogen ion concentration.

Pharmacological actions: Hypophosphatemia may occur after severe dietary deprivation of phosphorus, in primary hyperparathyroidism, in vitamin D deficiency, in patients with phosphaturia (isolated or as a part of a widespread disorder of tubular reabsorption in the form of Fanconi syndrome) and in the rare syndrome of familial hypophosphatemic rickets with vitamin D resistance. The hypophosphatemia severely interferes with calcification of the osseous matrix, leading to osteomalacia or rickets. The hypophosphatemia of primary hyperparathyroidism is without a direct metabolic effect, although some years ago it was believed to be responsible for hypercalcemia.

Hyperphosphatemia is seen in hypoparathyroidism and in renal failure. A relatively high serum inorganic phosphorus level is also seen in active acromegaly. In renal failure, the elevated plasma phosphorus level depresses that of calcium and is also responsible for the widespread metastatic calcification of soft tissues.

Therapeutic uses: (1) Neutral phosphate mixture is used to treat hypercalcemia and familial vitamin D resistant rickets with low serum phosphate. It is prepared as follows: disodium hydrogen phosphate 3.66 gms, sodium dihydrogen phosphate 1 gm., orange syrup 16 ml., water to make 60 ml. Sixty millilitres of this solution give 1 gm. of phosphorus and is generally administered three times a day by mouth. It can also be used intravenously. (2) Disodium hydrogen phosphate is a saline purgative. Its use has been described in Chapter 37.

MAGNESIUM METABOLISM

Magnesium is an important constituent of the human body. The average amount of body magnesium in an adult weighing 70 kg. is about 2,000 m. equiv. Of this, approximately 50-70 per cent is in bones, 1 per cent is in the ECF and the remaining is intracellular, where it is concentrated mainly in the mitochondria. Bone acts as a magnesium reservoir during depletion. The plasma magnesium levels vary from 1.5 to 2.0 m. equiv./1.; nearly 33 per cent of this is bound to plasma proteins. Cardiac and skeletal muscles, liver, brain and kidneys contain appreciable amounts of magnesium.

Physiological and pharmacological actions: Magnesium has important effects on the central nervous system and myoneural transmission. It is a depressant of the central nervous system and low magnesium levels may evoke increased irritability, confusion and convulsions. Magnesium also possesses local anaesthetic activity and depresses myoneural transmission by reducing the quantal release of acetylcholine and by antagonizing its depolarizing effect at the motor end plates, and by reducing the excitability of muscle cell membrane. Administration of large doses of magnesium resulting in levels over 10 m. equiv./1 may produce fatal respiratory paralysis.

The central nervous system and the myoneural depression produced by magnesium can be antagonized by calcium. It is paradoxical that independently both calcium and magnesium are central depressants; however, the central narcotic effect of excessive magnesium is antagonized by calcium.

The cardiac muscle appears to be less susceptible to the depressant effect of magnesium than the skeletal muscle. However, heart block, increased PR interval and widening of QRS complex may result if the plasma levels exceed 10 m. equiv./1.

Magnesium causes peripheral vasodilatation. Small doses usually produce flushing while large doses may result in hypotension. Whether this effect is secondary to relaxation of vascular smooth muscle or ganglionic blockade is uncertain.

Magnesium is a co-factor of many vital enzymes like membrane—ATPase. An activating role for magnesium has also been postulated in the uptake and storage of catecholamines within the osmophilic granules of the sympathetic nerve endings and in the activation of ribosomes by the messenger RNA.

Absorption, fate and excretion: Magnesium and calcium probably have common transport mechanisms across the gut and the renal tubules. The daily dietary intake of magnesium in Americans is 20-40 m. equiv. and of this, nearly 1/3rd is absorbed from the gastrointestinal tract. Low levels of magnesium intake enhance calcium absorption and vice versa. Magnesium is mainly excreted by the kidney by glomerular filtration. Increased urinary excretion occurs in hyperparathyroidism and in diuresis induced by glucose and by diuretics. Parathyroid hormone appears to be essential for both gastrointestinal and renal tubular reabsorption of magnesium. Only 3 to 5 per cent of filtered magnesium appears in urine, the rest is reabsorbed. Renal impairment may cause magnesium retention and this may lead to toxicity even with orally administered magnesium containing antacids and purgatives.

Magnesium deficiency: The various causes of the deficiency are severe and continued diarrhoea or fistulous discharge, chronic alcoholism, intestinal malabsorption, hyperparathyroidism, diuretic therapy and renal tubular acidosis. Magnesium deficiency has also been encountered in aldosteronism and during recovery from renal tubular necrosis.

Magnesium deficiency is characterised by weakness and mental disturbances like restlessness, and increased aggressiveness. Involuntary movements, convulsions and rarely tetany may develop.

The serum magnesium level may be as low as 0.8 m. equiv./1; the bone and muscle magnesium levels are also reduced. A low serum level, however, is not necessarily diagnostic of magnesium deficiency, as even hypoalbuminaemia, by reducing the concentration of the bound form, may result in low serum magnesium levels.

The urinary output of magnesium is very low and it fails to increase even on magnesium loading. When magnesium deficiency is secondary to excessive renal loss, urinary magnesium levels are obviously above normal.

Magnesium deficiency is usually associated with low level of intracellular potassium, particularly in the skeletal muscle. The plasma potassium levels are usually normal.

Acute hypomagnesemia stimulates PTH secretion; however, chronic hypomagnesemia accompanied by hypocalcemia impairs PTH synthesis or release. Such patients show symptoms similar to hypoparathyroidism; however, they do not respond till magnesium is given. Although PTH stimulates renal reabsorption of magnesium, hyperparathyroidism is accompanied by hypomagnesemia.

Histological changes seen in magnesium deficiency in animals include deposits of calcium in the broad ascending limb of Henle's loop (an unusual form of nephrocalcinosis) and myocardiac sclerosis. However, significantly low serum calcium levels are often encountered in clinical magnesium deficiency.

Magnesium deficiency can conveniently be treated by daily administration of approximately 300 m. equiv. of magnesium given as magnesium hydroxide mixture. Even patients in whom magnesium deficiency is secondary to diarrhoea, the diarrhoea may improve with this therapy. If oral medication is not possible, 20 ml. of 50 per cent magnesium sulfate can be given slowly, intravenously.

Therapeutic uses of magnesium salts:

(a) **As antacids and osmotic purgatives:** See Chapter 37 and 38.

(b) **As central depressant:** Magnesium sulfate is still occasionally used to control seizures in acute nephritis and toxaemia of pregnancy. A 20 per cent solution is usually administered intramuscularly or intravenously for this purpose. In toxaemia of pregnancy parenteral magnesium sulfate also achieves a moderate reduction in blood pressure. Care must be taken to keep a calcium preparation ready to counter excessive central depression with magnesium.

(c) **In magnesium deficiency:** Discussed previously.

(d) Some cases of digitalis cardio-toxicity resistant to potassium therapy respond to magnesium administration.

(e) **Local uses:** Magnesium sulfate in the concentration of 25 to 50 per cent in glycerine is used topically for alleviation of inflammation. It acts by exerting an osmotic effect. Magnesium sulfate, when given orally in poisoning with soluble barium salts, forms insoluble barium sulfate. Magnesium oxide is also an ingredient of *universal antidote*. Concentrated solution of magnesium sulfate is sometimes used rectally to reduce intracranial tension.

PARATHORMONE (PTH): It is secreted by the chief cells of the parathyroid glands. It is secreted as an 84 amino-acid polypeptide but is cleaved in the plasma into a large and a small fraction. The larger fraction (MW 6000) is biologically inactive but is the one which is largely measured by the radioimmunoassay of PTH in plasma. The smaller fraction is biologically active but much less reactive immunologically.

Physiological and pharmacological actions:

(1) **Gastrointestinal tract:** It promotes the active absorption of calcium and phosphorus. The presence of vitamin D is necessary for this action of PTH.

(2) **Bones:** It stimulates osteoclastic resorption of old bone and thus, resorption of calcium and phosphorus from bone into the extracellular fluid. Vitamin D is necessary for this action of PTH. PTH does not influence the ionic exchange of calcium occurring between the extracellular fluid and the newly laid down bone mineral.

(3) **Kidney:** (a) It promotes the reabsorption of calcium from the glomerular filtrate by the distal renal tubules. Only when the plasma calcium level rises as a result of the action of PTH, the urinary excretion of calcium increases.

(b) It increases the urinary excretion of phosphorus by decreasing its proximal tubular reabsorption and

(c) It also increases the urinary excretion of sodium, potassium, and citrate and decreases the excretion of hydrogen and magnesium by changing the tubular function.

(d) It is necessary for the synthesis of 1,25 D.H.C.C. by the kidneys.

The effect on the kidney is of more rapid onset than that on the bone.

All the actions of PTH are directed towards increasing the ionic calcium of the plasma and ECF. It probably also influences ion movements in other parts of the body.

Regulation of secretion: The rate of secretion of PTH is directly stimulated by a fall and inhibited by a rise in the ionic calcium of the plasma. Alterations in the plasma inorganic phosphorus level affect it only indirectly. The rate of secretion of

PTH is not affected by neurogenic influences or by other hormones.

Mechanism of action: PTH acts on the cell wall to (a) stimulate the formation of cyclic AMP and (b) increase its permeability to calcium ions which then move intracellularly. In the bone, it stimulates the conversion of mesenchymal cells into osteoclasts; further it inhibits the osteoblasts and hence collagen synthesis.

Hyper- and hypoparathyroidism: *Hyperparathyroidism* may be primary (due to a parathyroid tumour), secondary (due to secondary hyperplasia in patients with rickets, osteomalacia or chronic renal disease), or tertiary (where one of the hyperplastic glands in the secondary group becomes adenomatous and autonomous). Hyperparathyroidism of the primary and tertiary varieties is accompanied by hypercalcemia while in secondary hyperparathyroidism serum calcium level is subnormal. The effects of hyper and hypocalcemia have already been described. The excessive secretion of PTH in all the three groups leads to generalized bone disease with increased osteoclastic resorption, thinning of bones and cyst formations. It is called osteitis fibrosa generalisata.

Hypoparathyroidism is either primary, due to aplasia of the parathyroid glands or secondary, following surgical damage to the parathyroids. This causes retention of phosphorus and hypocalcemia with resultant symptoms. Tetany develops when plasma calcium level falls below 7 mg. per cent. Its two other effects, which are not explained by hypocalcemia, are cataract formation and calcification of basal ganglia.

Rarely, a calcitonin producing tumour (see below) may produce all the manifestations of hypoparathyroidism.

Absorption, fate and excretion: PTH given orally is hydrolyzed by the proteolytic enzymes. Given subcutaneously, its peak effect is seen in 18 hours and the response lasts upto 36 hours. It is partly degraded by liver and partly excreted in urine.

Adverse reactions: Hypercalcemia, along with its disadvantages, and anaphylactic reactions are the two important adverse effects of PTH.

Preparation and dosage: Parathyroid injection U.S.P. contains not less than 100 units of the calcium raising activity per ml. Dose: 40 units every 12 hourly by I.M. injection.

Assay of PTH: The hormone is bioassayed by its ability to raise the serum calcium levels in dogs. More sensitive and more specific radioimmunoassay method is now available.

Therapeutic uses: There is now no valid therapeutic use for PTH. Its use in hypocalcemic states has been supplanted by vitamin D and its metabolites. It is, however, useful in the diagnosis of pseudohypoparathyroidism, a rare condition in which the clinical and biochemical features are those of hypoparathyroidism but do not respond to PTH (end organ resistance).

CALCITONIN : Calcitonin is a polypeptide isolated from the mammalian thyroid and cells of the ultimobranchial bodies in lower vertebrates. Calcitonins from various animal species including the humans have been characterised and totally synthesized. They are all 32 aminoacid polypeptides although their aminoacid sequences are different. In humans, salmon calcitonin has the most potent pharmacological action.

In the thyroid, it appears to arise from C cells which lie in between the thyroid follicles. These cells are structurally similar to cells of the ultimobranchial bodies in lower animals. In the mammals, the ultimobranchial bodies fuse with the thyroid. In humans, C cells are also present in the parathyroids and the thymus. Hence thyroidectomy has no effect on plasma calcium level.

It lowers the plasma levels of calcium and phosphorus. It does this mainly by blocking the PTH induced bone resorption. Thus, the calcium from the circulation is shunted to bone. It also has a minor effect on the kidneys whereby it increases the urinary excretion of calcium, sodium, potassium and phosphorus; plasma magnesium is scarcely affected.

Calcitonin is secreted in response to increased plasma levels of ionic calcium. Its action of lowering plasma calcium level is rapid and of short duration.

The role of calcitonin in calcium homeostasis in man is not yet clear.

Therapeutic uses: Salmon calcitonin (Calcimar) in gelatin solution is available for i.m. use. It is very expensive. The recommended dose is 100 units a day. It has been found useful in initially alleviating hypercalcemic states such as those associated with hyperparathyroidism, vitamin D intoxication and osteolytic bone metastases. Calcitonin alone or with oral phosphate is the treatment of choice in Paget's disease.

VITAMIN D : The term vitamin D is applied to a group of related sterols which have the common property of preventing or curing rickets.

Chemistry: Many sterols on ultraviolet irradiation, develop the antirachitic property. They are fat soluble and have the same general structure (Fig. 64.1).

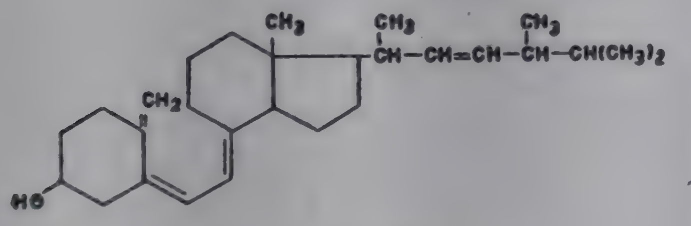


Fig. 64.1: Calciferol (D_2)

Irradiation of ergosterol gives rise to calciferol (Vitamin D_2) and of 7-dehydrocholesterol to cholecalciferol (Vitamin D_3). Dihydrotachysterol, a synthetic reduction product of tachysterol, also has similar properties.

7-Dehydrocholesterol exists in the secretion of sebaceous glands of humans and animals, which on exposure to sunlight is converted to vitamin D_3. Thus, vitamin D of animal origin such as in fish liver oil and irradiated milk is D_3 while calciferol or D_2 is the active agent in irradiated yeast and irradiated bread. Vitamin D_1 is a mixture of several sterols. In human beings D_2 and D_3 have similar actions, qualitatively and quantitatively.

Physiological functions and pharmacological actions: Many, if not all, of the metabolic actions of vitamin D are exerted by its active metabolite, 1,25 dihydroxycholecalciferol (1.25 DHCC), biosynthesized by the kidney and now considered to be a potent, renal, steroidal hormone. It is of interest to note that recently the plant *Solanum malacoxylon* has been shown to possess 1,25 DHCC in water soluble form and is responsible for an endemic disease in grazing animals. The main actions of vitamin D are on the gastrointestinal tract, bone, kidneys and muscle.

In general, vitamin D helps to maintain the normal concentrations of calcium and phosphate in the plasma and extracellular fluids and promotes normal bone matrix calcification.

(a) **Gastrointestinal tract:** Vitamin D stimulates the absorption of calcium and phosphorus from the intestines. 1,25-DHCC after entering the mucosal cell, binds to the nuclear chromatin and initiates the synthesis of messenger RNA. This mRNA stimulates the ribosomes to synthesize a carrier protein required for the transport of calcium. This gastrointestinal action of vitamin D is antagonized by corticosteroids which block its activation in the liver (see below).

(b) **Bone:** 1,25-DHCC acts directly on skeleton and causes bone resorption; this is its primary action on the bone. This effect on bone resorption is histologically identical with that seen following parathyroid hormone but 1,25-DHCC is more potent than PTH in this respect. The enhanced bone mineralization following vitamin D therapy is believed to be mainly due to the rise of the plasma calcium and phosphorus concentrations.

(c) **Kidneys:** The actions of vitamin D on the kidney are still not very clear. However, it appears that it acts directly on the renal tubule leading to increased reabsorption of calcium and phosphate. Thus, the action of 1,25-DHCC on the kidney somewhat resembles the intestinal action of this hormone.

(d) **Muscle:** The uptake of radiocalcium by the sarcoplasmic reticulum is subnormal in vitamin D deficiency; it can be corrected by vitamin D administration. Clinically, the proximal myopathy is a prominent feature of vitamin D deficiency.

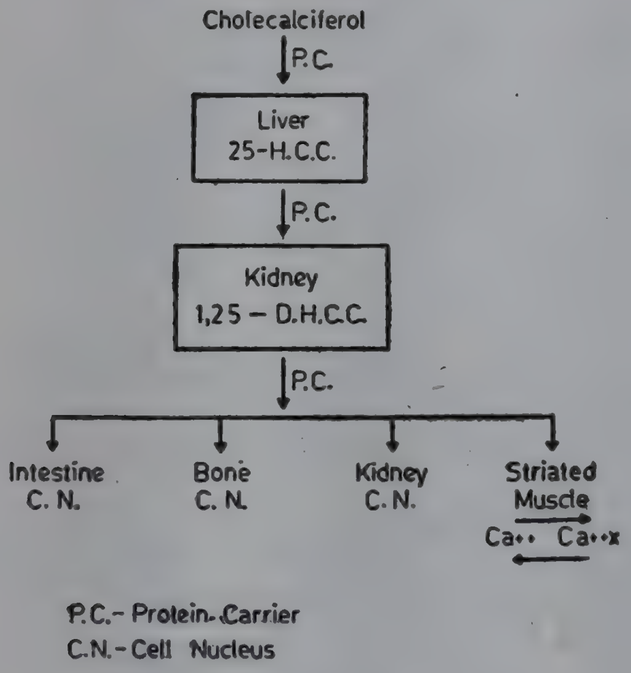


Fig. 64.2: Actions of vitamin D.

Mechanism of action: 1,25-DHCC acts on the nucleus of the target cells and stimulates transcription of messenger RNA to promote synthesis of specific proteins.

Absorption, fate and excretion: Given orally, vitamin D is adequately absorbed in the presence of bile salts, in the distal small bowel. The absorption is defective in individuals with obstructive jaundice and in those with steatorrhoea. Mineral oil prevents absorption of dietary vitamin D. It is stored mainly in the body fat. In the plasma, all of it is bound to proteins and none is excreted in urine.

The liver converts cholecalciferol to 25, hydroxycholecalciferol (25, H.C.C.). This latter compound is converted by the kidneys (in the presence of P.T.H.) to the most active vitamin metabolite 1,25 dihydroxycholecalciferol (1,25 D-H.C.C.). The hepatic conversion of cholecalciferol to 25, H.C.C. is strongly inhibited by glucocorticoids. Renal output 1,25 D.H.C.C. is stimulated by a diet poor in either calcium or phosphorus but is inhibited by a high phosphate diet. It is also stimulated by prolactin.

Assay: Bioassay of vitamin D depends upon its ability to prevent or cure rickets in young rats. In recent years, biological material has been assayed for its vitamin D content by isolating the latter chromatographically and measuring it by spectrophotometry. An international unit of vitamin D is the specific biological activity of 0.025 μg. of pure calciferol (1 mg. calciferol = 40,000 I.U.).

Adverse reactions: Hypervitaminosis D is the term used to describe the ill-effects of chronic administration of excessive amounts of vitamin D. It is likely to occur in an individual with normal vitamin D sensitivity receiving 50,000 units or more per day for prolonged periods. Such doses have often been used empirically in adults with disorders such as rheumatoid arthritis and cutaneous tuberculosis not associated with vitamin D deficiency. Such large doses of vitamin D give rise to generalized decalcification of bones, hypercalcemia, hyperphosphatemia, hypercalciuria and metastatic calcification. The clinical features of hypercalcemic state have already been described.

Preparations and dosage: (i) Calciferol I.P. occurs as colourless crystalline powder insoluble in water. It contains 40,000 units of antirachitic activity per mg.

(ii) Shark liver oil with vitamin D I.P. contains 6,000 units of vitamin A activity and 1,000 units/ml. of antirachitic activity. Dose: 0.5 to 1.5 ml. daily orally in divided doses.

(iii) Concentrated vitamin D solution I.P. contains 10,000 units of antirachitic activity per g.

(iv) Vitamin D_2 oily injection (Calciferol injection) N.F. contains 600,000 units of vitamin D_2 in an oily solvent.

(v) For other preparations containing both vitamin A and D, e.g. cod-liver oil, and shark liver oil see Chapter 69.

Therapeutic uses: The daily requirement of vitamin D in infants, children and adults is about 400 units. This must be remembered while prescribing vitamin D supplements to infants and children whose 'vitaminized' food may already be giving them their daily requirements. Children with dark skin need more vitamin than those with fair skin.

Human breast milk has always been thought to be poor in its vitamin D content and to supply only 4% of an infant's daily requirements. However, recent work indicates that it contains more vitamin D than was hitherto supposed. Most of it is in the form of water soluble vitamin D sulfate. The site of sulfation is not known. One teaspoonful of codliver oil gives about 650 U (85 U/g.) while 1 g. halibut liver oil contains 3,000 U of vitamin D.

Deficiency of vitamin D is now rare in the economically advanced countries except in immigrants from the developing countries. It is still common, especially in children, in countries like India. It is largely due to poor intake of vitamin D rich foods like milk, butter and eggs. It must be noted that the sun rays which induce vitamin D activity in the skin are in the ultraviolet range and can get absorbed by atmosphere, by glass and by buildings. Vitamin D deficiency can also occur in obstructive jaundice and steatorrhoea.

Vitamin D deficiency leads to rickets in children and osteomalacia in adults with low plasma inorganic phosphorus, normal or low plasma calcium, hypocalciuria, hyperphosphaturia and aminoaciduria. All these are rapidly reversible on administration of physiological amounts of vitamin D. In patients with obstructive jaundice and steatorrhoea large doses of vitamin D, given parenterally, are needed.

For routine use, calciferol (D_2) is the preparation of choice. Its uses are:

(1) **For prevention and treatment of vitamin D deficiency:** There is hardly any store of vitamin D at birth and the therapy is recommended from the first month. If the diet is deficient in older children, the daily requirement can be easily supplied by a teaspoon of cod-liver oil. Excessive administration must be avoided as rickets is less dangerous than hypercalcemia.

Fully developed rickets in children and osteomalacia in adults are best treated with parenteral administration of a single intramuscular injection of 600,000 units of calciferol repeated 4-6 weeks later, if the blood chemistry so indicates. Simultaneously, calcium must also be prescribed in order to avoid initial hypocalcemia following vitamin D and to provide calcium for the skeleton.

Parenteral administration of a single intramuscular dose of 600,000 units is desirable in patients with chronic obstructive jaundice in order to prevent vitamin D deficiency.

Routine prophylatic administration of calciferol (600,000 units once in 6-12 months) may be desirable in patients on long-term therapy with anticonvulsants.

(2) **Vitamin D resistant rickets and osteomalacia:** This term is applied to rickets and osteomalacia not due to vitamin D deficiency but due to a variety of disorders such as chronic renal insufficiency, renal tubular disorders and certain hereditary diseases including hypophosphatasia. Vitamin D in large doses (upto 50,000 U I.M. daily) is required to bring about healing of bone lesions in such patients. Vitamin D requirements for patients with steatorrhoea with bone disease fall midway between those with vitamin D deficiency and those with vitamin D resistant rickets. Neutral phosphate is also used to treat vitamin D resistant rickets associated with low serum phosphate level.

(3) **In hypoparathyroidism:** Calciferol

is the drug of choice in the treatment of hypoparathyroidism. Daily doses of 50,000 to 250,000 units are recommended.

(4) Vitamin D may be used to counter the effect of corticosteroids on the intestinal absorption of calcium in patients on prolonged corticosteroid therapy.

The synthetic analogues **l-hydroxycholecalciferol** (1-HCC) and 1,25-DHCC have been evaluated clinically in chronic renal failure, hypoparathyroidism, osteomalacia, osteoporosis and some type of non-nutritional rickets. In chronic renal insufficiency both these compounds are effective in very small doses (less than a μg daily) in correcting the biochemical and radiographic abnormalities. In cases of hypoparathyroidism, these compounds have an advantage over conventional vitamin D therapy, due to the relatively rapid onset of action and the similarly rapid loss of action should hypercalcemia occur.

DIHYDROTACHYSTEROL (DHT) : This is also known as A.T. 10 (Anti-tetanic preparation No. 10). Its properties are somewhat similar to those of calciferol and it can cure rickets. The drug mobilizes calcium from the skeleton, increases the gastrointestinal absorption of calcium and promotes the urinary excretion of calcium and phosphates. It can be given orally as well as intramuscularly.

The drug has certain advantages over vitamin D_2 and D_3. 25 Hydroxy-DHT is the active metabolite, (on bone and intestines) and need not be converted to its 1,25 dihydroxy metabolite. This is of great advantage in patients with advanced chronic renal disease.

FLUORIDE

The fluoride ion which is widely distributed in nature is of medical interest because of its toxicity as well as its possible clinical applications. It can enter the human body through edible plants, drinking water, fluorine containing pesticides, contaminated food additives and by inhalation of fluoride dusts and gases.

Pharmacological actions: With the exception of its actions on the teeth and bones in certain circumstances, the actions of fluoride can be classified as toxic.

Children who drink water containing fluorine (1 part per million) have been shown to develop permanent teeth which are resistant to the development of caries. Topical application of fluoride solution to the teeth after eruption is claimed to reduce the decay.

The action of fluoride on bones is discussed below.

Fluoride inhibits several enzymes and diminishes tissue respiration and anaerobic glycolysis in excised organs. It is a useful *in vitro* anticoagulant.

Absorption, fate and excretion: Fluoride is absorbed from the gastrointestinal tract, the lungs and the skin. In the body, fluoride can be detected in all tissues but is preferentially deposited in bones and teeth. It is excreted mainly by the kidneys and in small amounts by the sweat glands, the lactating breast and the gastrointestinal tract.

Adverse reactions:

(1) *Acute poisoning*: Acute poisoning results from ingestion of insecticides containing fluoride salts. The symptoms are due to irritation of the gastrointestinal tract (nausea, vomiting, abdominal pain and diarrhoea); due to hypocalcemia caused by binding of plasma calcium (increased irritability of the central nervous system); and due to medullary depression (fall of blood pressure and respiratory paralysis). Death is due to respiratory paralysis or cardiac failure.

Treatment is symptomatic and consists of stomach wash with lime water, intravenous fluids, intravenous calcium and treatment of respiratory and cardiac failure.

(2) *Chronic poisoning* : Chronic fluoride

poisoning gives rise to two main changes: osteosclerosis and mottled enamel. Osteosclerosis consists of an increase in density and calcification of bones and varies greatly in severity. Mottling affects only the developing teeth, teeth which have already erupted being spared.

Therapeutic uses: (1) Fluoridation of water is now an accepted public health measure for prevention of dental caries.

(2) Sodium fluoride by mouth in the dose of 30-50 mg. per day is used in osteoporosis (together with vitamin D) and in Paget's disease, with some benefit.

Section XIV : Miscellaneous

65 Pharmacotherapy of Gout and Rheumatoid Arthritis

Gout is a disease which is associated with an inherent abnormality of purine metabolism resulting in over-production of uric acid. It is characterized by acute attacks of pain and swelling of one or more joints. In untreated cases, uric acid in the form of mono-sodium biurate gets deposited in the cartilage of joints and ears, subcutaneous tissues, bursae and even in kidneys. Chronic degenerative complications are due to uric acid deposition and associated diseases like diabetes mellitus, hypertension and atherosclerosis. The pathogenesis of acute attack which could be precipitated by various factors including drugs is not clear and hence, its treatment still remains purely empirical.

Uric acid is synthesized by oxidation of exogenous or endogenous purines and is the normal excretory product in man. The plasma uric acid level normally varies between 3 and 6 mg. per cent. In patients with gout, the serum uric acid level shows persistent marked elevation. Usually, a serum level of 8.0 mg.% in asymptomatic patients indicates the need for therapy.

In the treatment of gout, drugs can be administered either,

(i) to give immediate symptomatic relief during the acute attack of gouty arthritis e.g. colchicine, phenylbutazone, indomethacin and corticosteroids, or

(ii) to decrease the hyperuricemia. This is achieved by (a) the uricosuric drugs which increase the excretion of uric acid e.g. sulphinpyrazone, probenecid and (b) the metabolic inhibitors e.g. allopurinol.

DRUGS USED DURING ACUTE STAGE

COLCHICINE is a highly effective and specific compound used in the treatment of acute gouty arthritis. The drug is administered orally in doses of 1 mg. followed by 0.5 mg. every two hours until pain is relieved or diarrhoea starts. It relieves pain in most cases within 24-48 hours. If taken early in the attack, it can arrest the attack immediately or may even prevent it. The total amount of colchicine required generally varies between 4 to 8 mg. Administered in small doses of 0.5 to 2 mg. daily, it can reduce the frequency of attacks and hence, it can also be used in maintenance therapy along with uricosuric drugs.

Mechanism of action: Colchicine produces arrest of mitosis in metaphase. However, the mechanism by which it terminates the acute attack of gout is not known. It has been suggested that colchicine relieves the acute attack by inhibiting phagocytosis of urate cystals by leukocytes: this decreases the inflammatory reaction.

Adverse reactions: Commonly, it produces gastrointestinal upset and diarrhoea. In case of troublesome diarrhoea, camphorated tincture of opium may be prescribed. Occasionally, it may cause anemia and leucopenia. Drug tolerance to colchicine is not known. Colchicine is rapidly degraded by exposure to light and loses its therapeutic efficacy. Because of the troublesome diarrhoea, many workers prefer phenylbutazone to colchicine.

PHENYLBUTAZONE : This is an analgesic and anti-inflammatory drug. It is described in detail in Chapter 9. It is administered orally in a dose of 200 mg. thrice daily. It can relieve pain in 8-12 hours. It also possesses uricosuric property but is not recommended for chronic use because of its serious toxicity.

INDOMETHACIN : This analgesic drug is discussed in Chapter 9. Given in the dose of 25-50 mg. 4-8 hourly, it can promptly relieve pain. However, the incidence of intolerance is high. The drug can be administered as 100 mg. suppositories at night.

GLUCOCORTICOIDS : ACTH and glucocorticoids can be used in very severe cases which may be refractory to colchicine or phenylbutazone. They are not to be used routinely, as their action is not specific and the relapse rate of acute arthritis is very high following the withdrawal of these compounds. Prednisolone is given in the dose of 30-40 mg. on the first day and the dose is then progressively reduced by 5-10 mg. every day.

When a large joint such as the knee joint is affected, aspiration and intra-articular injection of hydrocortisone acetate may give dramatic relief.

In severe cases with excruciating pain, analgesics like pethidine in doses of 100 mg. parenterally may be necessary until pain is relieved by other agents. Addiction liability of such drugs, however, prevents their repeated use.

DRUGS USED IN LONG TERM THERAPY

These drugs are useful because: (a) they either promote the excretion of uric acid (uricosuric agents) or (b) they decrease its synthesis.

Although these drugs do not prevent the acute attack totally, they decrease its incidence and probably diminish the incidence of renal damage and other complications due to urate deposition.

(a) **Uricosuric drugs:**

PROBENECID (Benemid) : This uricosuric agent is generally given orally usually in doses of 0.5 g. three times daily. In low doses, it causes a decrease in distal tubular secretion of uric acid and in larger therapeutic doses, it increases the excretion by blocking tubular reabsorption of uric acid. Given for some months, the blood uric acid may return to normal levels with significant mobilization of gouty tophi. The drug is remarkably non-toxic and is well tolerated. Probenecid is not to be used in combination with phenylbutazone and salicylates as the efficacy of such combination is much less than that of the individual agents. Occasionally, it causes dyspepsia, skin rashes and very rarely nephrotic syndrome.

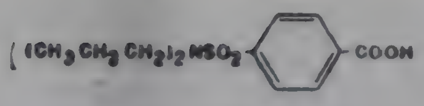


Fig. 65.1: Probenecid.

ETHEBENECID : This is closely related to probenecid and there is very little to choose between the two except the cost of therapy.

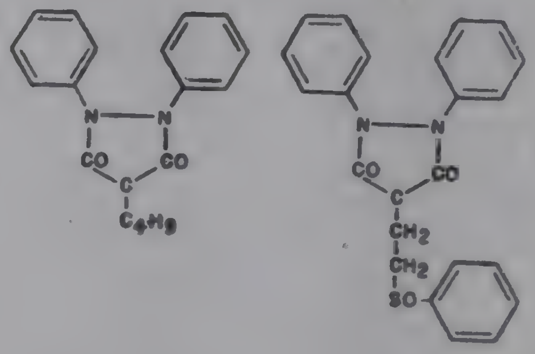


Fig. 65.2: Phenylbutazone. Sulphinpyrazone.

SULPHINPYRAZONE (Anturan) : This is a sulfoxide derivative of phenylbutazone with slight anti-inflammatory activity but marked uricosuric property. It is administered orally in doses of 100-200 mg. thrice daily. The daily dose should not exceed 600 mg. The common toxicity includes vomiting, upper abdominal discomfort and skin rashes. Rarely, it can aggravate an existing peptic ulcer and may produce bone marrow depression. As compared to phenylbutazone, it is less toxic and is well tolerated.

Neither probenecid nor sulphinpyrazone is effective in the presence of impaired renal function. These drugs should be avoided during or soon after an acute attack as symptoms are often exacerbated.

Other uricosuric drugs include the benzofuran compounds, **benziodarone** and **benzbromarone.** These drugs are potent and are claimed to be effective even when GFR is reduced to 25-50% of the normal. They are under evaluation.

Aspirin, an analgesic, is known to relieve joint pains. It is discussed in detail in Chapter 9. Although it has a uricosuric action, the dose required for persistent uricosuria is large, 3-5 g. daily, and adverse effects with such a large dose make it unsuitable for the treatment of gout. Further, in smaller doses it acts as antiuricosuric and also blocks the uricosuric effect of other drugs. Salicylates, in any form, therefore, should be avoided in gout.

(b) Uric acid synthesis inhibitors:

ALLOPURINOL (Zyloric) : It is 4-hydroxypyrazolo 3, 4 d-pyrimidine and is a very useful long term agent in the treatment of gout.

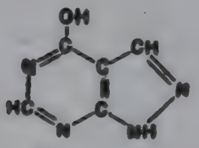


Fig. 65.3: Allopurinol.

Mechanism of action: During the purine metabolism, the purine nucleotides are degraded to hypoxanthine and xanthine. These purine bases are then finally oxidised to uric acid by the action of xanthine oxidase. Allopurinol and its degradation product alloxanthine, are potent inhibitors of xanthine oxidase and hence, they (1) interfere with the oxidation of the oxypurines, hypoxanthine and xanthine to uric acid, (2) lower serum and urine uric acid in patients with gout, and (3) increase the excretion of hypoxanthine and xanthine in the urine. Both these oxypurine compounds are cleared rapidly by the kidney and hence, there is less hazard of crystallization of uric acid in the kidneys. This is an advantage over uricosuric agents. (Fig. 65.4).

Adverse reactions: The incidence of adverse reactions is low. Occasionally, it can give rise to allergic manifestations. Sometimes, it also causes nausea, vomiting, diarrhoea, leucopenia and hepatic damage. These changes are generally reversible. Haemosiderosis is a rare but dangerous complication of allopurinol therapy.

Preparation and dosage: It is supplied as 100 mg. tablets. It is started in a small dose (50 mg per day) and increased gradually in 2-3 weeks upto 300 to 600 mg. daily in divided doses.

Therapeutic uses: Allopurinol is used for controlling hyperuricemia. It is most useful in cases with renal failure where uricosuric drugs are rendered ineffective, and in the presence of urate calculi and large tophi. Allopurinol can be combined with the uricosuric drugs.

The drug is also used in the treatment of secondary hyperuricaemia following the use of cytotoxic agents in the treatment of leukemia and lymphoma. As xanthine oxidase is responsible for the metabolism of the cytotoxic drug 6-mercaptopurine, simultaneous administration of allopurinol markedly prolongs the action of 6-mercaptopurine; hence, the dose of this drug should be reduced to approximately 1/3 to 1/4 of

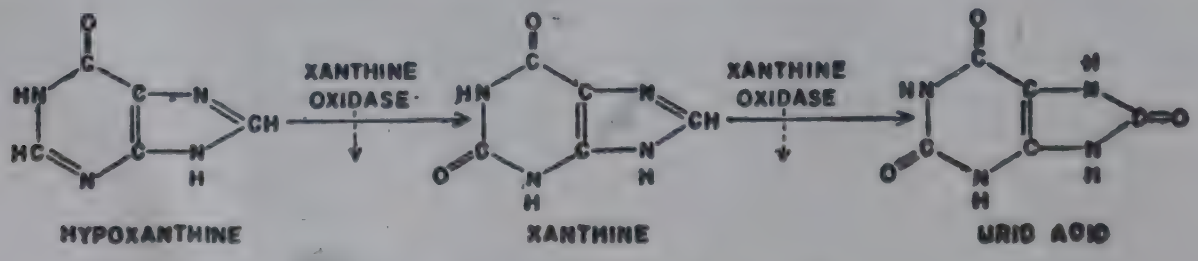


Fig. 65.4: Synthesis of uric acid.

the usual to avoid serious toxicity.

Other measures in gout: With all the drugs used in between the attacks, a fluid intake sufficient to yield daily urinary output of at least 2 litres and the maintenance of a neutral or slightly alkaline pH are desirable to prevent any possible renal damage. This is particularly important during hot weather and in the tropics.

As an acute attack may be precipitated by a surgical procedure in a gouty patient, colchicine should be used prophylactically during the postoperative period. Further, colchicine or phenylbutazone is also recommended as prophylactic drug during the early stages of treatment with uricosuric drugs and allopurinol, as these drugs may precipitate an acute attack by mobilizing uric acid deposits.

Certain other drugs like thiazide diuretics, pyrazinamide, cytotoxic agents, and alcohol taken on empty stomach tend to raise the blood uric acid level which may precipitate an attack of gout.

With the introduction of these newer agents in the treatment of gout, rigid dietary control is now rarely necessary though the treatment and prevention of obesity is important.

PHARMACOTHERAPY OF RHEUMATOID ARTHRITIS

Of all the rheumatic disorders, rheumatoid arthritis still remains a formidable disease, being capable of producing severe crippling deformities and functional disability. The etiology of this disease is not known and the natural course varies considerably from person to person. The disease can undergo a spontaneous remission and it is difficult to forecast the outcome of the disease in a particular individual; hence, the evaluation of new drug therapy becomes difficult.

The drug therapy of rheumatoid arthritis is presently empirical and it aims at:

(a) relief of pain and control of inflammation.

(b) improvement and maintenance of function, and

(c) prevention of deformity.

Although none of the drugs available at present can confer everlasting benefits and induce permanent remission, drugs are of great value in achieving symptomatic relief and functional improvement of the affected joints. The drugs used are:

I. *Anti-inflammatory and analgesics*: aspirin, propionic acid derivatives, phenylbutazone and indomethacin.

II. *Anti-inflammatory without analgesic action*: glucocorticoids, ACTH.

III. *Miscellaneous* (*with unknown action*): penicillamine, gold salts, chloroquine.

IV. *Immunosuppressants*: azathioprine.

Anti-inflammatory analgesics: Detailed pharmacology of salicylates, phenylbutazone, indomethacin, propionic acid derivatives and fenamate compounds is discussed in Chapter 9. These drugs relieve pain, decrease the swelling and help to improve the joint movements. This facilitates the practising of exercises designed to promote the maintenance of function and the prevention of deformity. Aspirin still remains the drug of choice and is usually given in the dose of 3-5 g. daily. The danger of gastrointestinal bleeding following aspirin is probably exaggerated and, in itself, should not deter a physician from continued clinical use of this useful drug. Since phenylbutazone has prolonged action, a single dose at bedtime often relieves the night pain and the early morning stiffness satisfactorily. The pyrazole compounds should not be combined with gold salts as both drugs may depress the bone marrow. Both phenylbutazone and indomethacin can be given as suppositories per rectum so as to avoid gastric irritation.

Various propionic acid derivatives have been used as substitutes for aspirin. These are ibuprofen (200-400 mg. thrice daily), alcofenac (1 g. thrice daily), naproxen (250 mg. twice daily) and ketoprofen (50 mg. thrice daily) given with food. They have analgesic-anti-inflammatory activities and probably produce less toxicity as compared to aspirin, phenylbutazone and indomethacin. Single dose of naproxen 500 mg. taken at bed-time may also be effective. Clinically they do produce relief of pain and diminish swelling. However, although the definite incidence of their adverse reactions is not yet known, all of these can cause gastric irritation or overt gastrointestinal haemorrhage. They are less potent anti-inflammatory agents than aspirin.

Gold salts: Water soluble gold preparations like sodium aurothiomalate, aurothiosulfate and aurothioglucose have been shown to produce some beneficial effect in rheumatoid arthritis. Sodium aurothiomalate (Myocrisin) is the usually employed drug. It is given in the dose of 10-25 mg. I.M. weekly for prolonged period or 50 mg. I.M. weekly for 20 injections. The mechanism of action of gold salts is not known. They produce marginal but definite clinical improvement accompanied by lower titres in the Rose Waaler test. These drugs, unlike corticoids, do not produce radiological evidence of benefit.

Absorption, fate and excretion: Sodium aurothiomalate given intramuscularly is rapidly absorbed and diffuses throughout the body within 15 minutes. Gold salts are cumulative and the metal has been reported to remain in the kidney for many years after injection. It gets distributed in the kidney, liver, spleen and other tissues including syncytial lining cells. The drug is excreted in urine, about 15-25 per cent being excreted during the first week.

Adverse reactions: Like other heavy metals, gold salts can cause various toxic manifestations. The important effects are dermatitis, albuminuria, mucosal ulceration, bone marrow depression and liver damage. The incidence of toxicity is fairly high and careful clinical and hematological supervision must be exercised during the therapy. Gold toxicity is treated with prednisolone (10-20 mg. daily), dimercaprol and chelating agent d-penicillamine.

Antimalarials: Chloroquine and related drugs have been shown to produce marginal benefit in the active disease. Their mechanism of action is not known. Pharmacology of chloroquine is discussed in Chapter 50. Chloroquine phosphate is administered in the dose of 250 mg. daily. The improvement is usually seen after 3 months of therapy and prolonged treatment (6-12 months) is necessary for full benefits. Like gold salts, chloroquine does not affect the radiological changes. Chloroquine, because of its specific affinity for the tissues containing melanin, gets accumulated in the pigmented tissues of the eye, leading to retinopathy and irreversible visual impairment. It is necessary, therefore, to carry out periodic ophthalmic examination during prolonged chloroquine therapy; the total weekly dose of chloroquine phosphate should not exceed 1,750 mg.

Glucocorticoids: Soon after the discovery of cortisone, it was shown that the drug produces dramatic effects in rheumatoid arthritis. The remission lasts as long as the drug is used. During such prolonged therapy, adverse effects can be minimised by using small daily doses e.g. 5-7.5 mg. of prednisolone. However such small doses may not be beneficial in all cases. The newer synthetic 'supersteroids' do not offer any distinct advantages over prednisolone. Pharmacology and adverse effects of glucocorticoids are discussed in Chapter 60.

d-Penicillamine: This is a sulphur containing amino acid used as a chelating agent and discussed in detail in Chapter 66.

Apart from chelation, it causes a split in the rheumatoid factor and also selectively reduces the serum levels of certain immunoglobulins. Although its exact mechanism of action is not known, the drug induces relief in patients with rheumatoid arthritis who have failed to respond to other therapy.

d-Penicillamine is given in the dose of 500 mg. daily for two weeks and then increased at fortnight intervals to 1 g. and then to 1.5 g. daily. Unfortunately, the incidence of adverse reactions is very high, making the withdrawal of the drug necessary in 30 per cent of the patients (see Chapter 66).

Immunosuppressive agents: Various alkylating agents like azathioprine, cyclophosphamide and antimetabolites like methotrexate have been claimed to be beneficial in inducing remission in rheumatoid arthritis. This is because rheumatoid arthritis is suspected to be an autoimmune disease and these drugs act as immunosuppressants. It should be noted, however, that all these agents are highly toxic and the danger of toxicity outweighs the possible marginal benefit claimed for these drugs. Immuno-suppressants, therefore, have presently no place in the routine management of rheumatoid arthritis.

Choice of drug therapy: In all the cases, aspirin in adequate doses should be tried first. Majority of the cases respond to salicylates or other drugs from this group. It may be noted, however, that the non-steroidal anti-inflammatory drugs do not influence the acute phase protein response and hence, unlike the glucocorticoids, do not influence the level of the E.S.R. Maximum therapeutic benefit is generally achieved in 7-10 days. Aspirin may be continued, if needed, with other analgesics such as codeine, dextropropoxyphene or pentazocine in patients in whom pain is a prominent feature. If control of symptoms is inadequate even after giving adequate doses of salicylates or if new joints become involved, a more potent (though more toxic), anti-inflammatory-analgesic drug such as phenylbutazone or indomethacin may be used. If relief is still inadequate, only then may the other drugs be tried: penicillamine, gold salts, chloroquine and immunosuppressants (in that order). These drugs are potentially dangerous and offer only marginal benefits. They may be added if non-steroidal anti-inflammatory agents fail to produce adequate response or in cases with moderately severe disease affecting many joints with accompanying constitutional disturbances, mild anaemia and minimal radiological changes. In such circumstances, minimum possible doses should be used and regular periods of rest for 2-3 months should be introduced in between the courses. Salicylates, gold or antimalarials are not likely to be of much help in severe progressive disease with marked constitutional symptoms and deformed joints. In such cases, judicious use of low dose corticosteroid therapy along with salicylates may modify the destructive course of the disease; the prognosis, however, is not so good. Immunosuppressants are reserved for intractable disease.

Supportive therapy: Rheumatoid arthritis being a chronic disease, general supportive therapy including good nutrition and attention to psychological aspect is as important as drug therapy. Both physical and mental rest are essential. During the acute stage the rest must be complete, along with proper splinting of affected joints. A firm mattress with only one firm, low pillow should be allowed at bed time. Antianxiety and antidepressants may be necessary along with analgesics to control anxiety and insomnia. In most patients with active disease, bed rest for 4 weeks followed by 2-6 weeks of planned rehabilitation is advisable. Immobilization of inflamed joints is carried out for 4 weeks followed by active exercises. Light exercises should also be prescribed during complete rest, to be carried out in the recumbent position for improving circulation and correcting faulty posture. Proper exercises and physiotherapy during the recovery stage are essential for achieving maximum benefit.

Although definite focal sepsis must be

treated promptly, removal of "suspected teeth or tonsils" will not cure the disease; on the contrary, removal of teeth will affect the nutrition and mental getup of the patient.

Anemia usually responds to iron therapy. Usefulness of muscle relaxants is highly doubtful; so also of non-specific protein or fever therapy. There is no doubt, however, that local intra-articular injection of hydrocortisone is useful for controlling inflammation. Usually, hydrocortisone acetate suspension is given in the dose of 25-50 mg. for big joints and 5-10 mg. for small joints once every 3-4 weeks. Number of injections would depend upon the response. The drug may also be injected extra-articularly into painful ligaments, tendons and inflamed bursae with beneficial results. The duration of relief obtained varies from a few days to a few weeks. Apart from this, patient may also need help to combat the serious social and economic problems that are usually associated with such a chronic and disabling ailment.

66 Metals and their Antagonists

The heavy metal salts, which formerly constituted the major part of the chemotherapeutic armamentarium, are currently of interest mainly from the toxicological point of view. It is, therefore, proposed to discuss only briefly their therapeutic applications and to emphasize their toxicity in humans.

Pharmacological actions: The organic and the inorganic salts of heavy metals possess astringent, corrosive and caustic properties on local application. They also act as general protoplasmic poisons and impair the cell function. The heavy metal salts, in very small quantities, are lethal to several Gram-positive and Gram-negative organisms and this effect is referred to as the oligodynamic action.

Adverse reactions: All the heavy metals are cumulative and potentially toxic. They cause damage to various organs like the liver, the kidney and the gastrointestinal tract. Rapidly proliferating tissues such as the bone marrow, the gastrointestinal mucosa and other delicate cells such as neurons and renal tubular cells are also affected.

Although some heavy metals probably owe their toxicity to inhibition of sulfhydryl group of enzymes, other mechanisms involving formation of complexes with amino, imidazole, phosphate and carboxyl groups have not been completely ruled out.

ARSENIC: Arsenic, though ordinarily presumed to be a metal, is in fact a metalloid. It is a notorious poison since ancient times. Arsenical compounds can be divided into (i) inorganic arsenicals, used mainly as rodenticides, herbicides and insecticides and (ii) organic arsenicals, used in the chemotherapy or trypanosomiasis, amoebiasis and trichomoniasis. Organic arsenicals, once used extensively, are no longer favoured in the treatment of syphilis.

The organic arsenicals can be further subdivided into trivalent and pentavalent compounds. The pentavalent compounds, which are anionic in character in body fluids, probably penetrate the host cells less readily than the trivalent compounds and consequently, have a higher therapeutic index than the latter. Although it is claimed that the therapeutic activity of pentavalent compounds is partly due to their reduction into trivalent forms *in vivo*, trivalent compounds as such are not used in therapeutics because of their high toxicity.

Absorption, fate and excretion: Soluble arsenical salts are rapidly absorbed from the gut. Absorption may also occur through the skin from the ointments containing arsenic. Arsenic is stored mainly in the gut, liver, spleen, kidney and lung; small amounts are also present in the brain and the skeletal muscle. It also accumulates in bones and hair.

Very minute quantities of arsenic have been detected in majority of the vertebrates. The physiological role of such minute amounts is, however, not known.

Arsenic is mainly excreted in urine and feces. Urinary excretion usually starts within 2 to 8 hours after oral administration and continues for 8 to 10 days. Cumulative poisoning can thus occur on repeated ingestion of small amounts. Small amounts also appear in sweat and in saliva. Arsenic deposited in hair and bones is retained for years.

Arsenic poisoning: Arsenic poisoning is usually homicidal but occasionally, may occur accidentally, particularly in children, following ingestion of arsenical herbicides or insecticides. It may be either acute or chronic.

Acute arsenical poisoning is characterised by severe gastrointestinal irritation, vomiting, diarrhoea, circulatory collapse and renal failure. The gastrointestinal symptoms usually begin within 1 hour after ingestion of the arsenical compound but may occasionally be delayed upto 12 hours. The symptomatology markedly resembles that seen in cholera and a careful distinction is essential before institution of treatment. In severe poisoning, death may occur within 24 hours.

The treatment consists of correction of fluid and electrolyte imbalance and administration of the specific antidote, dimercaprol. Prophylactic antibiotic therapy is advocated to prevent secondary infection. Hemodialysis may be necessary in the event of total renal shutdown.

Chronic arsenic poisoning: Chronic arsenic poisoning has a relatively insidious onset and this is the main reason for its common use as a poison for homicidal purposes. The early symptoms are weight loss, anorexia, fatigue and diarrhoea or constipation. Later, other manifestations such as edema, particularly of eyelids and ankles, hyperpigmentation of the skin, especially the eyelids, neck, nipples and the axillae, and dermatitis including exfoliative, and inflammatory lesions of the mucous membranes, may occur. There may be loss of hair, finger nails become brittle and may eventually drop off. The breath has a garlic odour. Late manifestations of arsenic poisoning include jaundice, aplastic anemia and peripheral neuropathy leading to numbness, paraesthesiae, wrist and foot drop. Necrosis and degeneration of renal tubules and liver cirrhosis may develop. Arsenical encephalopathy has also been reported. Hyperkeratosis of palms and soles may undergo malignant change in the form of basal cell carcinoma; chemical analysis of hair and bones is often helpful in establishing the diagnosis.

The treatment of chronic arsenic poisoning consists of prolonged administration of the specific antidote, dimercaprol. However, arsenical aplastic anemia and jaundice usually do not respond, while arsenical encephalopathy is relieved only partially if the therapy is instituted promptly.

Preparations: The organic arsenical compounds used in the treatment of amoebiasis and trypanosomiasis are discussed in Chapter 51 and 52 respectively.

Therapeutic uses: Apart from the uses mentioned earlier, arsenicals are also used as weed killers and rodenticides.

Externally, arsenic trioxide has been applied as a paste, with cocaine or morphine, to the cavities of carious teeth to destroy the nerves before filling the teeth. Leakage of the agent may, however, cause necrosis of gum or bone.

LEAD: Lead compounds have hardly any therapeutic use. They are, however, used in various industries and are responsible for causing chronic lead poisoning in workers. Poisoning with the metal may also occur from lead projectiles, particularly lead shots embedded in skin or muscle.

Lead salts internally and externally exert an astringent action which is due to the formation of lead proteinate. Externally, lead subacetate is sometimes employed as a constituent of lotions used as soothing astringent applications.

Absorption, fate and excretion: Lead is absorbed to the extent of 9 to 12 per cent from the gut. It is also absorbed from the respiratory mucous membrane, as observed in workers who inhale lead fumes or dust. Respiratory absorption of lead is more dangerous than its gastrointestinal absorption where the liver acts as a barrier. Organic lead compounds like tetraethyl and tetramethyl lead are absorbed more rapidly by the respiratory mucosa than the inorganic compounds. In addition, they can also be absorbed from the intact, unbroken skin.

Following absorption, inorganic lead is mainly associated with erythrocytes. High concentrations are initially present in liver and kidneys. Subsequently, it is mobilised from these sites and deposited in bones in the form of insoluble tertiary lead phosphate, mainly in epiphyseal regions of growing long bones, where it can be detected radiologically. High phosphate intake and vitamin D favour the deposition of lead into bones whereas a high calcium and low phosphate intake, parathyroid hormone, dihydrotachysterol, iodides and metabolic acidosis cause mobilization of lead from the bones and its subsequent elimination in urine. Lead deposited in bones does not contribute to the toxicity.

Lead present in the gut is eliminated fairly rapidly. But, lead deposited in soft tissues and in bones is excreted very slowly by the kidneys, within a period varying from a few weeks to years. A small amount also appears in sweat.

Lead poisoning: This can be acute or chronic.

Acute lead poisoning: Acute lead poisoning is a rare entity, usually secondary to ingestion of soluble lead compounds like lead acetate. It is characterised by a metallic taste in mouth, symptoms of gastrointestinal irritation and occasionally, acute nervous system symptoms like paraesthesiae, muscle cramps and weakness. The stools have a dark colour owing to the presence of lead sulfide. An acute hemolytic crisis resulting in severe anemia and hemoglobinuria may occur and usually proves fatal.

Treatment of acute lead poisoning consists of prompt gastric lavage and administration of cathartics like magnesium sulfate to hasten the evacuation of lead from the gut and use of calcium and phosphate salts and chelating agents for elimination of lead from the circulation. Antispasmodics like atropine are used to relieve the intestinal colic while parenteral fluids and vasopressor agents are employed in the management of shock.

Chronic lead poisoning: Chronic lead poisoning is commonly seen in young children from sucking lead paint or lead toys, in workers engaged in printing and paint industries, and in petroleum industry where organic lead compounds like tetraethyl lead and tetramethyl lead are added to petrol as anti-knock remedies. The manifestations of chronic lead poisoning are:

(a) **Gastrointestinal tract:** The commonest symptoms are a persistent metallic taste in mouth, anorexia, constipation and episodes of abdominal pain due to intestinal colic, termed '*lead colic*'. Chronic constipation due to lead poisoning is often ignored and itself enhances the absorption of lead from the gastrointestinal tract. Another feature of diagnostic importance is the grayish *lead line* which appears along the gingival margin and is due to periodontal deposition of lead sulfide; this may not be seen in the presence of good dental hygiene.

(b) **Skeletal muscles:** Muscle weakness and increased fatiguability leading subsequently to paralysis is described as 'lead palsy'. The paralysis may cause unilateral wrist drop and less commonly, foot drop. The extraocular muscles are also occasionally involved. Long standing paralysis may produce atrophy or contractures. The exact location of the lesions is not yet ascertained but degenerative changes in the motorneurones and their axons, and impairment of high energy phosphate metabolism of the affected muscles, have been incriminated as probable causes.

(c) **Haemopoietic system:** Punctate basophil stippling of erythrocytes has been regarded as a cardinal manifestation of chronic lead poisoning. It must be pointed out, however, that stippling up to a limit of 800 to 1000 per million erythrocytes is physiological and it is only when this count exceeds 35,000 per million erythrocytes, that the suspicion of lead poisoning should be entertained. Further, absence of stippling does not rule out lead intoxication. Other hemopoietic disturbances are a microcytic hypochromic anemia, jaundice secondary to increased hemolysis, and excretion of abnormal products of porphyrin metabolism in urine. The latter phenomenon is attributed to a defective hemoglobin synthesis.

(d) **Central nervous system:** Central nervous system toxicity is commoner in children than in adults and is described as '*lead encephalopathy*'. It is initially manifested by increased irritability, headache, restlessness and tremors, followed by delirium and convulsions or by lethargy and coma. The convulsions are repetitive and resemble those seen in grand mal epilepsy although occasionally they may be unilateral. Visual disturbances may occur and stippling of the retina adjacent to the optic disc is claimed to be an early diagnostic sign. Lead encephalopathy has a mortality of 25 per cent and nearly 1/4th of the survivors develop permanent mental deficiency.

Organic lead compounds produce acute central nervous system toxicity in adults, with similar manifestations.

(e) **Miscellaneous:** Mild renal damage as signified by the presence of casts and proteins in urine, occurs occasionally in chronic lead poisoning.

Treatment: The drug of choice in the treatment of chronic lead poisoning is the chelating agent, calcium disodium edetate, which is discussed later. A less useful agent is penicillamine. Dimercaprol is of little value. Chelating agent therapy often fails to relieve lead colic which, however, can be controlled by the administration of antispasmodics, and calcium gluconate, 2 g I.V. Convulsions are best treated with paraldehyde or diazepam. Increased intracranial tension can be relieved by mannitol or by lumbar puncture.

ANTIMONY: This metal resembles arsenic in chemical and biological properties. Antimony, however, is more irritant locally and certain antimony salts like antimony potassium tartrate possess a powerful emetic activity.

The trivalent and pentavalent compounds are absorbed slowly from the gut. The trivalent compounds are more firmly bound to erythrocytes than the pentavalent compounds and consequently, exhibit lower plasma levels and slower renal excretion than the latter.

The toxic effects of antimonials resemble those of arsenic. Dimercaprol is protective against the toxic effects of organic forms but its efficacy against the toxic effects of inorganic antimony compounds is doubtful.

Therapeutic uses of antimony compounds in protozoal diseases, in filariasis and schistosomiasis are discussed in Chapters 52 and 54 respectively. Antimony potassium tartrate is occasionally given intravenously as 1 per cent solution in the treatment of resistant cases of mycosis fungoides. The first two doses are 2.5 ml. and 3.5 ml. followed by 5 ml. thrice weekly.

BISMUTH: Bismuth salts, formerly popular in the treatment of syphilis are now rarely employed in this condition. Compounds like bismuth carbonate, bismuth subsalicylate, bismuth subgallate and bismuth subnitrate are sometimes used in the treatment of diarrhoea because of their mild astringent and mechanical coating effects. These are discussed in Chapter 36. Bismuth preparations used in the chemotherapy of amoebiasis are discussed in Chapter 51.

Bismuth salts have been used in a variety of skin conditions like lichen planus, localised scleroderma, lupus erythematosus and vitiligo with doubtful results. These salts have also been claimed to be useful in local application in the treatment of piles and condyloma acuminata.

Because of the rarity with which bismuth is used systemically, intoxication due to bismuth is rare. Chronic poisoning may lead to fever, gastrointestinal disturbances, urticaria, stomatitis, nephritis and nephrosis. A metal line on the gums is often seen. Dimercaprol is an effective antidote.

MERCURY: The organic mercurials are used as antiseptics, preservatives, spermicides and diuretics. These are discussed in Chapter 55 and 34 respectively.

Acute mercury poisoning is usually due to accidental ingestion of mercuric chloride and other readily ionizable mercury salts. It is characterised by severe gastrointestinal irritation leading to electrolyte disturbances and peripheral circulatory collapse. The patient complains of a metallic taste in mouth, excessive salivation and inflammation of gums. Arrhythmias may develop due to the toxic effect of mercury on the myocardium. Later, marked renal impairment occurs due to its nephrotoxic action leading to death. Secretion of mercuric ion into the gut and its reabsorption prolong the toxic effects of the metal.

Treatment is directed towards removal of mercuric ions from the gastrointestinal tract and towards its quick renal elimination. The former is achieved by administration of proteins in the form of raw eggs or milk, which form non-toxic proteinates and by giving medicinal charcoal in suspension. This is followed by gastric lavage, though it is of doubtful value after the first 15 minutes or so, since mercury is rapidly absorbed by the mucous membrane of the alimentary tract. Sodium formaldehyde sulfoxylate which reduces the mercuric ion to the less soluble mercurous form may also be used. About 200 to 250 ml of 5 per cent solution is employed for gastric lavage and an equal volume is left in the stomach.

Dimercaprol is an effective antidote for countering the systemic toxicity. However, to be maximally effective, it must be injected within first hour or two after poisoning. It is ineffective in the event of extensive renal damage for which hemodialysis is indicated. Recently, acetyl penicillamine has also been used in acute mercury poisoning. Supportive treatment with parenteral fluids, treatment of shock and prophylactic use of antibiotics for prevention of secondary infection are also instituted.

Chronic mercury poisoning is manifested by increased irritability, tremors, headache, easy fatiguability, stomatitis, colitis, increased salivation and dermatitis. Electrolyte imbalance, liver damage and renal damage are also seen. Dimercaprol is an effective antidote. Supportive therapy for correction of electrolyte disturbances may be necessary.

An allergic manifestation seen in children due to systemic absorption of topically applied mercurial antiseptics is termed *Pink disease* or acrodynia. Its manifestations include marked swelling and erythema of the extremities with sweating, itching and polyarthritis. It responds to therapy with acetyl penicillamine. Fever and skin rashes of various types have also been reported in adults using mercurial antiseptics topically.

SILVER: The silver salts used as antiseptics are discussed in Chapter 56. Silver salts are not used for systemic therapy. Continued application of silver salts and especially of silver nitrate to mucous surfaces or open wounds leads to *argyria*, a bluish black discoloration of the skin due to deposition of granules of a silver compound in the connective tissue. The condition looks ugly but is not injurious to health. It disappears very slowly.

GOLD: See Chapter 65.

CADMIUM: This metal is employed in a wide range of manufacturing processes. Acute cadmium poisoning, when due to ingestion, is characterised by severe gastrointestinal irritation and circulatory collapse; acute poisoning due to inhalation of cadmium fumes results in cough, sore throat, vertigo, dyspnoea, cyanosis and bronchopneumonia. Chronic cadmium poisoning causes a characteristic yellow pigmentation of teeth (the yellow ring of cadmium), anosmia, emphysema and proteinuria. Both dimercaprol and EDTA are not recommended for treatment as they may further aggravate the kidney damage caused by cadmium. Calcium gluconate, administered I.V. in the early stages, is claimed to be of some value.

Medicinally, a 1% suspension of cadmium sulfide has been used in the treatment of seborrhoeic dermatitis and dandruff. However, selenium sulfide 2.5% suspension is usually preferred.

THALLIUM: This metal was employed as the acetate for depilation. It is, however, highly toxic and may lead to marked neurological disturbances on systemic absorption. The drugs used for the treatment of systemic thallium toxicity are dimercaprol and dithiocarb.

Heavy Metal Antagonists

The toxicity of the heavy metals is attributed to their ability to form complexes with important biological radicals like the sulfhydryl, the hydroxyl, the carboxyl, the amino and the imidazole. Affinity for sulfhydryl group leads to inhibition of vital SH-containing enzymes. Inhibition of various enzymes leads to the toxic effects. Attempts were, therefore, made to develop organic compounds which would have a high affinity for the metallic ions. Such drugs would combine with the metallic ions to produce relatively non-toxic and easily water-soluble complexes which are subsequently eliminated by the kidneys. The process by which these organic compounds combine with the metals to form relatively stable nonionized ring complexes is called *chelation* (chele=claw), the compounds being designated as *Chelating agents*. The heavy metal antagonists used in therapeutics are:

I. DIMERCAPROL (BAL): Dimercaprol, or British Anti-Lewisite, was synthesized by Stocken and Thompson during the World War II to ensure protection against poisoning by the arsenical war gases such as Lewisite. Because the compound contains two SH groups, it is chemically a dithiol (Fig. 66.1).

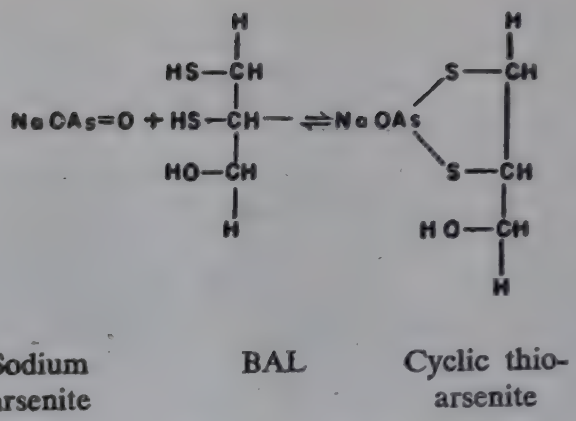


Fig. 66.1: Mode of action of BAL

Pharmacological actions: Dimercaprol forms poorly dissociable complexes with arsenic, mercury and cadmium ions and thus protects the sulfhydryl (SH) enzymes. In case of mercury and cadmium, the dimercaprol-metal complex further reacts with another molecule of dimercaprol to form a still more stable, inactive complex.

Even though the dimercaprol-metal complexes are poorly dissociable, some amount of dissociation does occur *in vivo*, causing the release of the toxic metal in the active form. To overcome this drawback, the dosage schedule of dimercaprol is adjusted in such a way that an excess of free drug is always present in the body to bind the free metal released as a result of dissociation.

Dimercaprol not only protects the sulfhydryl enzymes from inactivation by heavy metals but also reactivates the inhibited enzymes. However, the ability of dimercarpol to achieve reactivation is limited by the amount of the metallic ion present in circulatioin, and by the duration of poisoning. Thus, dimercaprol fails to protect or reactivate the sulfhydryl enzymes if administered late or in the presence of overwhelming amounts of the metal.

Dimercaprol itself inhibits enzymes such as peroxidase, catalase and carbonic anhydrase in which the heavy metals constitute prosthetic groups.

Absorption, fate and excretion: Following the intramuscular administration of dimercaprol, peak plasma levels are reached in about 2 hours and the drug is entirely metabolised within 6 to 24 hours. A part of the drug is excreted as a glucuronide in urine.

Adverse reactions: Doses of dimercaprol in the range of 4 to 5 mg per kg body weight produce a variety of adverse effects in approximately 50 per cent of patients. These include nausea, vomiting, headache, burning sensation in the mouth and eyes, lachrimation, sialorrhōea, paraesthesiae of the extremities, muscle pain and muscle spasm. It can also cause anginal pain, tachycardia and hypertension. Injection of BAL is painful and can cause sterile abscesses and drug fever.

Dimercaprol-metal complex dissociates more readily in an acidic medium. The urine, therefore, should be made alkaline during dimercaprol therapy to protect the kidneys from the toxic effects of the released free metal.

The use of dimercaprol is contraindicated in the presence of hepatic damage and in iron poisoning, as it forms a toxic complex with iron. Dimercaprol increases the urinary excretion of cadmium but the kidneys are likely to be damaged by the metallic ion. It should be used with caution in hypertensive individuals.

Preparation: Dimercaprol injection I.P. is a sterile solution of dimercaprol in a mixture of benzyl benzoate and arachis oil. It has a strong characteristic smell. The content of dimercaprol is between 90 and 110 mg per ml. It is given deep intramuscularly.

Therapeutic uses: Dimercaprol is useful in the treatment of acute poisoning due to arsenic, mercury, gold, antimony, bismuth and thallium.

In severe cases of arsenical and gold poisoning, 3 mg of the drug is given per kg. body weight, intramuscularly, at 4 hourly intervals for the first 2 days, at 6 hourly intervals on the third day, and twice daily for the next 10 days or until the recovery is complete. In case of gold poisoning, the maintenance dose may have to be administered for as long as 3 months. Smaller doses (2.5 mg./kg.) are used in milder cases.

Dimercaprol is effective in protecting the eyes from the effects of accidental contamination by arsenical vesicants. Complete recovery is usually achieved if 5 to 10 per cent oily solution of dimercaprol is instilled into the conjunctival sac within 5 minutes of contamination.

In acute mercurial poisoning, dimercaprol is administered initially in the dose of 5 mg. per kg. followed by 2 or 3 injections of 2.5 mg per kg during the next 12 hours, or until recovery is assured.

In patients with Wilson's disease allergic to penicillamine. dimercaprol is given in the dose of 2.5 mg per kg twice daily for first 2 days; followed by 2 days rest and this course may be repeated as long as necessary. The drug causes a moderate increase in the urinary excretion of copper in this condition.

II. d-PENICILLAMINE: This compound, a monothiol (containing one SH group), is prepared by alkaline hydrolysis of benzyl penicillin. Chemically, it is beta, beta-dimethylcysteine.

Pharmacological actions: Penicillamine forms a water soluble complex with copper, mercury and lead ions and thus facilitates their excretion in urine. Like dimercaprol, it inhibits a number of enzymes, including transaminase and desulfhydrase which have one of these metals as the prosthetic group.

Penicillamine is well absorbed on oral administration and rapidly excreted in urine.

Adverse reactions: The administration of d-penicillamine may occasionally cause toxic effects which include headache, sore throat, fever, rash, nausea, ecchymoses, lymphadenopathy, leucopenia, thrombocytopenia, agranulocytosis, proteinuria and a reversible nephrotic syndrome. Loss or impairment of the sense of taste can be very upsetting. Usually, this is reversible on stopping the drug. Allergic reactions occur occasionally and patients who are sensitive to penicillin may have a similar reaction to penicillamine.

Children and young women, receiving penicillamine therapy may rarely develop iron deficiency. The drug causes pyridoxine deficiency, and optic neuritis responding to pyridoxine has been reported.

Preparation: d-Penicillamine is a white powder with a characteristic odour, freely soluble in water. It is available in capsules containing 250 mg of the base equivalent to 300 ml of the hydrochloride.

Therapeutic uses:

(a) **Hepatolenticular degeneration** (Wilson's disease): Wilson's disease is a rare, hereditary disease of copper metabolism characterised by degenerative changes in the basal ganglia and cirhosis of the liver. The copper content of the liver, brain and other tissues is grossly increased, the total serum copper and ceruloplasmin copper content are reduced and the urinary excretion of copper is enhanced. The Kayser-Fleischer ring, a brownish pigmented ring at the corneal margin, is diagnostic of this condition. It is generally believed that the accumulation of copper is responsible for the symptoms.

Treatment is directed towards reducing the total body copper. This is achieved by administration of penicillamine, given in conjunction with a high protein, low copper diet with potassium sulfide (20 mg thrice daily with meals). The latter precipitates dietary copper in an insoluble form and thereby reduces its absorption from the gastrointestinal tract. Cationic exchange resins may be employed for the same purpose.

Penicillamine is administered in the dose of 0.9 to 1.8 g. daily. Depending on the urinary levels of copper, the dose may be subsequently increased to 4 to 5 g daily and continued indefinitely.

Penicillamine therapy results in a dramatic improvement in some of the patients, while others fail to recover despite a significant increase in the urinary excretion of copper. The response, therefore, probably depends upon the degree of irreversible structural damage.

Penicillamine has been found to be of some value in the treatment of acute lead and acute mercury poisoning. It is, however, ineffective against tetraethyl lead poisoning and being a monothiol, is less efficacious than dimercaprol in mercury intoxication. It has also been claimed to be useful in cystinosis, cystinuria, and hemosiderosis.

(b) **Rheumatoid arthritis:** See Chapter 65.

III. ACETYL d-PENICILLAMINE: This drug, a less toxic but weaker chelating agent than d-penicillamine, has been shown to be particularly effective in mercury poisoning. It is administered in the dose of 1 g daily in 3 or 4 divided portions, for 10 days. The course may be repeated after a week's interval.

IV. SODIUM CALCIUM EDETATE AND DI-SODIUM EDETATE: The calcium sodium and the disodium salts of ethylene diamine tetra-acetic acid (EDTA) form stable and highly water soluble complexes with many divalent and trivalent metallic ions and owe their therapeutic application to this chelating property. (Fig. 66.2).

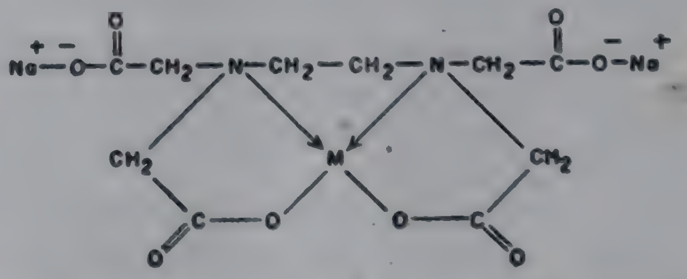


Fig. 66.2: Mode of action of di-sodium edetate 'M' stands for chelated metal.

The calcium sodium salt has a high affinity for lead, while the disodium salt exhibits a high affinity for calcium. The affinity of these chelating agents for other metals like sodium, magnesium and potassium is much less and this permits their selective application in the treatment of lead poisoning and hypercalcemia respectively.

Absorption, fate and excretion: Both the salts are poorly absorbed from the gastrointestinal tract and have to be given parenterally, usually by the intravenous route. They are excreted almost completely within 24 hours, both by glomerular filtration and tubular secretion.

Adverse reactions: Besides thrombophlebitis, these agents cause nausea, diarrhoea and toxic nephrosis. Oliguria and renal failure have been reported but generally, the damage is reversible following the cessation of drug therapy. Renal damage has been attributed to the free metallic ion released as a result of dissociation of the metal-chelate complex.

A febrile reaction, followed by myalgia, nausea, vomiting, histamine like reaction with rhinorrhoea, and lachrimation and dermatitis are the other adverse effects reported, particularly with the disodium salt. The disodium salt may also cause hypocalcemic tetany due to excessive chelation of calcium.

Preparations: (i) Sodium calcium edetate injection is a sterile 20 per cent w/v solution of anhydrous sodium calcium edetate in water. It should be diluted with normal saline or 5 per cent dextrose before intravenous administration.

(ii) Disodium edetate injection is available as 20 ml ampoules containing 3 g of the drug in aqueous solution.

Therapeutic uses:

(a) **Sodium calcium edetate:** It is used in the treatment of acute or chronic lead poisoning. It acts by exchanging its calcium for lead in the blood to form a stable, non-ionisable, water-soluble lead compound which is rapidly eliminated in urine. This exchange between lead and calcium is selective because other metals such as iron, copper and cobalt are more strongly bound to tissue proteins and hence, not available for exchange.

In acute lead poisoning, the agent is given by slow intravenous infusion in the dose of 40 mg per kg twice daily, as a 0.5 to 3 per cent solution in normal saline or 5 per cent dextrose, for a maximum period of 5 days. The course may then be repeated after intermission of 2 to 3 days. Smaller doses are recommended in the presence of encephalopathy and increased intracranial pressure. In children, the dose should not be greater than 55 mg per kg. This should be divided into two portions and given by intravenous drip.

The salt can also be used as a diagnostic test for lead poisoning. A total dose of 75 mg per kg divided into 3 doses, is administered as 20 per cent solution by intramuscular injection with 1.5 per cent procaine. If the excretion of lead is more than 500 microgrammes per 24 hours, the ingestion of lead is concluded to be excessive.

Sodium calcium edetate has also been used in the treatment of porphyria and in poisoning with iron, cadmium and plutonium. Its efficacy for these purposes, however, is not established.

(b) **Di-sodium edetate:** The major use of this salt is in the treatment of hypercalcemia. It is administered by intravenous infusion in normal saline or 5 per cent dextrose in the daily dose of 50 mg per kg in adults and 60 mg per kg in children. The same dose is also used occasionally to counter digitalis-induced cardiac arrhythmias.

Di-sodium edetate has been used in the treatment of corneal opacities either by topical application after removing appropriate area of corneal epithelium, or by iontophoresis, and in the treatment of burns of the eye.

Di-sodium edetate, by removing calcium, can prevent blood clotting. A solution containing 1.5 g of the salt per 100 ml of 5 per cent dextrose can preserve 400 to 500 ml of blood for 3 to 4 weeks.

V. DITHIOCARB: This agent, administered orally in the dose of 2 g. daily for 7 days, preceded by an initial dose of 200 mg. intravenously, has been found useful in the treatment of nickel carbonyl poisoning and also to some extent in acute thallium poisoning and in Wilson's disease. The toxicity reported in animals includes visual disturbances and blindness.

VI. DESFERRIOXAMINE AND DIETHYLENETRIAMINE PENTAACETIC ACID (DTPA): These compounds which selectively chelate iron are discussed in Chapter 30.

67 Therapeutic Gases; Oxygen and Carbon-Dioxide

Apart from the anaesthetic gases, other gases of therapeutic importance are oxygen and carbon dioxide. Helium, an inert gas present in the atmosphere in minute amounts has also found therapeutic applications.

OXYGEN: Oxygen is essential for human survival. Inspired air contains 21 per cent of oxygen. It is carried in the body largely in combination with hemoglobin and a small quantity is transported in physical solution in plasma. With an increase in the ambient pressure, the amount of oxygen carried in the form of physical solution is progressively increased.

Effects of oxygen administration: Inhalation of 100 per cent oxygen in a normal subject produces the following effects:

I. *Ventilation*: Oxygen at atmospheric pressure initially depresses and later mildly stimulates the ventilation; the depressor effect is probably indirect, due to inhibition of the chemoreceptor activity. Oxygen also directly decreases the sensitivity of the respiratory centre to carbon dioxide. This effect is particularly apparent when the gas is given under more than one atmospheric pressure.

II. *Cardiovascular system*: In normal individuals, oxygen produces a slight reduction in the heart rate and a moderate decrease in the cardiac output. The coronary and the cerebral blood flow are probably reduced, while the pulmonary vessels are dilated. It does not modify the blood pressure significantly.

III. *Nitrogen concentration*: Inhalation of oxygen leads to a reduction in the partial pressure of nitrogen within the pulmonary alveoli, with its subsequent diffusion from the body cavities and blood into alveoli from where it is eliminated.

Methods of administration: Two types of equipment are available for administering oxygen.

(1) *Those that aim at ensuring the highest concentration of oxygen in the inspired air*: These include the oxygen tent and the various types of closely fitting aero-nasal masks with a non-return valve and either a reservoir bag or a demand valve on the oxygen supply. The tents are cumbersome and require careful vigilance particularly against fire. Masks are particularly useful at high altitudes and in the treatment of bronchial asthma, pulmonary edema and chronic pulmonary diseases. Because of the irritant effect of oxygen on the respiratory tract, oxygen in high concentration should be humidified by passing it through either a humidifier or a nebulizer. The old and widely followed method of bubbling the oxygen through a Wolff's bottle containing cold water has been shown to be valueless.

(2) *Those that aim at achieving a steady concentration, less than 60 per cent in the inspired air*: These include such simple devices as the nasal cannula and the nasal catheter (inserted through the nostril into the nasopharynx) and the more sophisticated equipment such as the Ventimask. This latter operates according to Bernoulli's principle: the pressure of a flowing gas is least where the rate of flow is greatest. If one injects oxygen through a small orifice, it attains great velocity but its pressure falls; it, therefore, sucks the room air from the surroundings and thus gets diluted. A flow of 1 to 6 litres of oxygen per minute through a cannula or a catheter ensures an oxygen concentration of 24 to 44 per cent in the inspired air. Larger flow rates of oxygen do not achieve higher concentrations of oxygen and are, therefore, wasteful of oxygen. The

Ventimask is available in three models designed to deliver oxygen at fixed concentrations of 24, 28 or 35 per cent.

Adverse reactions:

(a) **Respiratory tract:** Inhalation of oxygen in the concentration of 60 per cent or more for 36 hours or longer may damage the pulmonary epithelium and inactivate a substance (surfactant) secreted by the alveoli and which helps to keep the alveoli patent by reducing the surface tension within them; consequently, extensive pulmonary atelectesis may occur. This is especially likely to occur when high concentration oxygen therapy is used along with assisted mechanical ventilation and the arterial oxygen tension is allowed to remain above 150 mm. Hg. for prolonged periods. Administration of oxygen at a pressure greater than 1 atmosphere may occasionally cause respiratory distress in neonates, particularly in premature ones.

(b) **Central nervous system:** Inhalation of pure oxygen at pressures greater than 2 atmospheres may lead to paraesthesiae, mental disturbances, twitching, loss of consciousness and generalised convulsions, resembling those observed in epilepsy. The convulsions may develop within a few minutes or several hours after inhalation of the gas.

(c) **Carbon dioxide narcosis:** In patients with chronic obstructive lung disease, status asthmaticus, weakness of the respiratory muscles (from polyneuritis, poliomyelitis or myasthenia gravis), and in those with central respiratory depression from narcotic poisoning, head injury or raised intracranial tension, the alveolar ventilation is inadequate to prevent a rise in the arterial carbon dioxide tension ($PaCO_2$). With increasing hypercapnia (raised $PaCO_2$), the respiratory centre becomes progressively more tolerant of CO_2 and its activity is solely maintained by the stimulus of hypoxemia (hypoxemic drive) reflexly through the carotid and aortic bodies. A removal of this stimulus by oxygen administration reduces the ventilation still further with a consequent rise in $PaCO_2$. This gives rise to the syndrome of carbon dioxide narcosis with raised intracranial tension and clinically manifested by sweating, twitchings, drowsiness, convulsions, papilledema and coma. It is a potentially lethal condition.

(d) **Retrolental fibroplasia:** High arterial oxygen tension (over 100 mm. Hg.) interferes with the retinal blood supply and produces an occlusive proliferative retinal disease termed retrolental fibroplasia. This is observed mainly in premature infants. Retinal changes appear within 3rd to 6th week of life and may either regress or progress relentlessly to eventual blindness.

(e) Every oxygen appliance is a potential **fire hazard** and no naked flame, lighted cigarette or electric switch should be brought near a patient receiving oxygen.

Preparations: Oxygen I.P. is dispensed in a compressed state in cylinders painted black with a white shoulder. Cylinders of oxygen mixed with carbon dioxide are also painted black but have grey and white quarterings on neck and shoulder.

Therapeutic uses: The primary indication of oxygen therapy is hypoxia. Hypoxia may be defined as inadequate tissue oxygenation. Hypoxia, as said by Haldane, "not only stops the machinery but also wrecks the machine". The brain is probably the organ most sensitive to hypoxia, and irreversible damage usually results within 3 to 4 minutes of its onset. Hypoxic damage to the kidney, liver and heart is also seen. Hypoxia may be classified as:

I. **Hypoxic:** This is characterised by hypoxemia. For its causes, see below.

II. **Anemic:** Here, the oxygen carrying capacity of the blood is reduced due to deficiency of hemoglobin as in anemia or due to inability of the altered hemoglobin to take up oxygen as in methemoglobinemia, and carbon monoxide poisoning. In this variety, the oxygen tension in the arterial blood is normal but the 'oxygen content' is reduced.

III. **Stagnant:** This is due to excessive slowing of blood supply to the peripheral tissues as a result of inadequacy in peripheral circulation, e.g. in shock.

IV. **Histotoxic:** Here, the metabolic oxygen demand of the tissues may be increased abnormally as in thyrotoxicosis, salicylate poisoning and/or the tissue may be unable to utilise the available oxygen either as a result of paralysis of essential enzyme systems (cyanide poisoning) or due to a mechanical barrier (tissue edema).

A healthy person at rest, breathing room air with 21 per cent oxygen at a partial pressure of 160 mm. Hg., maintains the partial pressure of oxygen in the pulmonary alveoli (P_AO_2) at 100 mm. Hg. The oxygen in the alveoli equilibrates with the blood in the pulmonary capillaries and produces in the arterial blood a partial pressure of oxygen dissolved in the plasma (arterial oxygen tension, PaO_2) of 80-100 mm. Hg. and an oxygen saturation (SaO_2) of over 95 per cent. A reduction in the arterial oxygen tension is called *hypoxemia.* This must be distinguished from *hypoxia* which means inadequate tissue oxygenation. Hypoxemia generally (but not always) leads to hypoxia; on the other hand, hypoxia can arise from other causes than hypoxemia.

The carotid and the aortic bodies are the chemoreceptors which sense hypoxemia and stimulate breathing (mechanical ventilation) and the heart reflexly so that the hypoxemia tends to be corrected. In this process, the additional breathing effort and cardiac work increase the oxygen requirement of the body. At a certain stage, the body finds the increased ventilation and cardiac work uneconomical in terms of oxygen consumption and settles for a lower level of mechanical ventilation (breathing) even at the risk of continued hypoxemia. This is what commonly happens when a patient with chronic, obstructive, lung disease gets an acute chest infection and starts hyperventilating in order to compensate for the increase in the hypoxemia.

Hypoxemia can arise in several ways. These are:

(1) Reduction in the partial pressure of oxygen in the inspired air as at high altitudes.

(2) Alveolar hypoventilation i.e. failure to maintain the partial pressure of oxygen in the alveoli (P_AO_2) at the normal level. This occurs (a) in any condition which gives rise to rapid and shallow breathing e.g. right and left sided cardiac failure, asthma, acute pulmonary embolism, paresis or paralysis of the respiratory muscles (as in polyneuritis, poliomyelitis or myasthenia gravis); and (b) in patients with central respiratory depression as in narcotic poisoning, head injuries and raised intracranial tension. *In many of these conditions, the alveolar hypoventilation leads to hypercapnia (raised* $PaCO_2$). This has important therapeutic implications.

(3) Ventilation in excess of perfusion. This is seen in two types of situations: (a) hyperventilation in patients under anaesthesia and on certain types of respirators; and (b) emphysema where the destruction of alveolar septal walls produces large, over-ventilated but poorly perfused air sacs. In both groups of patients, the hyperventilation is manifested by diminished $PaCO_2$. *Hypercapnia does not occur.*

(4) Intrapulmonary shunting of blood. In this, large areas of the lung tissue are adequately perfused but their alveoli are not ventilated at all. As a result, unoxygenated blood passing through these capillaries mixes with the properly oxygenated blood coming from the well ventilated areas of the lung; this results in hypoxemia. It is seen in (a) pulmonary atelectasis due to bronchial obstruction or due to pleural diseases such as massive pleural effusion or pneumothorax; and (b) in diseases in which fluid collects in the alveoli viz., pneumonia, pulmonary edema and pooled secretions. *Hypercapnia does not occur in shunt diseases.*

(5) Venous admixture: In this, the alveolar ventilation is inadequate for a given level of pulmonary perfusion. This is seen (a) in all conditions giving rise to alveolar hypoventilation (already discussed); and (b) in conditions which produce an uneven distribution of ventilation. This latter mechanism occurs in almost all pulmonary diseases and is the prime reason for

hypoxemia in chronic, obstructive pulmonary disease. *Hypercapnia is liable to accompany hypoxemia in these groups of conditions.*

(6) Alveolo-capillary block to diffusion of gases as is seen in interstitial lung diseases. As carbon dioxide diffuses much faster than oxygen even in these patients, *hypoxemia is accompanied by hypocapnia.*

(7) Intracardiac right to left shunt as in cyanotic, congenital heart diseases.

(8) Decreased central-venous oxygen content from any cause especially shock. The severity of the effect of intrapulmonary shunting is largely determined by the degree of desaturation of the central venous blood.

Our understanding of hypoxemia and its treatment is incomplete without an understanding of CO_2 transport and disposal in the body. Carbon dioxide is one of the final metabolic waste products in the body and enters the blood through the peripheral tissue capillaries. In the blood, it is carried (1) dissolved in the plasma; it is this CO_2 which accounts for the partial pressure of CO_2 (CO_2 tension or PCO_2); (2) as carboxyhemoglobin in the red blood cells; and (3) as bicarbonate to which it is rapidly converted in the red blood cells with the help of the enzyme carbonic anhydrase. In the lungs, it diffuses rapidly across the alveolocapillary barrier into the pulmonary alveoli. The rate of washing out of carbon dioxide from the alveoli and hence from the blood, at a given rate of CO_2 production (i.e. at a given metabolic rate), is determined solely by the adequacy of alveolar ventilation. When more CO_2 is produced as a result of increased metabolic rate (as in fever), the mechanical ventilation (i.e. breathing) increases proportionately to wash out the excess of CO_2 and maintain the carbon dioxide tension in the alveoli (P_ACO_2) and in the arterial blood ($PaCO_2$) at the normal level of 30-50 mm. Hg. Whenever ventilation fails to increase proportionately to the rise in CO_2 production, the $PaCO_2$ is elevated above 50 mm. Hg. In any situation of hyperventilation, $PaCO_2$ falls below 30 mm. Hg. Thus, the $PaCO_2$ *level faithfully reflects the adequacy or otherwise of alveolar ventilation.* This has important implications in oxygen therapy. In any cardio-pulmonary disease where $PaCO_2$ is normal, it is safe to administer oxygen in high concentration without special precautions. In any condition accompanied by elevated $PaCO_2$, oxygen in high concentration tends to precipitate carbon dioxide narcosis; this has already been discussed in detail. These patients are, however, badly in need of oxygen which should not be withheld from them. Only, it should be administered in low concentration so that the hypoxemia is only partly corrected, unless they can also be given mechanical assistance to ventilation. In that case, they can be given oxygen in high concentration. Administration of sedatives and hypnotics makes these patients drowsy and abolishes their voluntary ventilatory drive; it can push them into CO_2 narcosis. So can the administration of depressants of the respiratory centre such as morphine.

The clinical recognition of 'hypoxia' is largely inferential. Hypoxia cannot be measured but has to be surmised by the presence of (a) a clinical situation known to produce hypoxia, and (b) hypoxemia which can be detected by measurement of PaO_2. In acute lung disease, hypoxemia can be clinically diagnosed in the presence of central cyanosis. Cyanosis is difficult to make out in anemic patients. In patients with chronic hypoxemia due to chronic, obstructive lung disease, it is difficult to clinically make out an increase in the hypoxemia such as occurs in a super-added acute chest infection. These patients then show signs of carbon dioxide narcosis or of right sided cardiac failure which should be taken as indications of increased hypoxemia. The other parameters useful in assessing a hypoxemic patient are (a) the clinical assessment of cardiac, circulatory and neurological status of the patient; and (b) laboratory measurement of hemoglobin, $PaCO_2$, acid-base and electrolyte status.

The results of oxygen administration are the best in situations where there is deficiency of oxygen in the inspired air as at high altitude. Breathing 100% oxygen is beneficial in this situation.

In cardiopulmonary disorders, the conditions maximally helped by oxygen therapy are those associated with alveolar hypoventilation, venous admixture and alveolo-capillary block. (Groups 2, 5, 6 above). Those in which $PaCO_2$ is elevated (Groups 2, 5) should be treated with oxygen in low concentration and the effect on the patient's clinical condition (and on the $PaCO_2$ if possible) should be watched carefully. Others can be safely treated with high concentration oxygen therapy. Conditions with an intrapulmonary shunt (Group 4) can be safely treated with and benefit from oxygen in high concentration. Conditions with ventilation in excess of perfusion (Group 3) are likely to show less benefit from oxygen therapy unless accompanied by an additional physio-pathological process likely to benefit markedly from it.

Administration of oxygen in high concentration to patients in shock (Group 8) merely increases the amount of dissolved oxygen in the plasma; though it may be small, it may be sufficient to tip the scales in patient's favour in this critical condition. Besides, the administration of oxygen in high concentration can relieve the pain of myocardial infarction, an important cause of shock.

In severe anemia, oxygen in high concentration does the same thing that it does in shock viz. that it adds that little extra dissolved oxygen which helps the critically ill patient.

In a cyanotic, congenital, cardiac disease such as Fallot's tetralogy (Group 7), the patient has hypoxemia and reduced arterial oxygen content despite the compensatory polycythemia. These patients tolerate their hypoxemia very well in the ordinary circumstances but need oxygen in high concentration during a chest infection and during surgery.

Oxygen is used by workers in pressurised spaces to reduce the inhaled nitrogen concentration and thus to prevent the decompression sickness. It is also commonly used during anaesthesia with the gaseous and the volatile general anaesthetic agents.

HYPERBARIC OXYGEN: According to Henry's law, the volume of the gas dissolved in a solution depends upon the tension (the partial pressure) of the gas present. Thus, the amount in plasma can be progressively increased by breathing oxygen at an absolute atmospheric pressure greater than one. The larger amount of oxygen present in the form of physical solution enables better tissue oxygenation. Hyperbaric oxygen is oxygen administered at higher than atmospheric pressure. It is administered by using a special chamber, filled with compressed air at higher than one atmospheric pressure and the patient breathes oxygen through a face mask or a mouth piece.

Inhalation of hyperbaric oxygen causes a reduction in the heart rate and the cardiac output and produces peripheral vasoconstriction. The retinal blood vessels are constricted. Blood pressure is not modified significantly. Hyperbaric oxygen is more toxic to the respiratory and the central nervous systems. Retrolental fibroplasia is another dangerous adverse effect. At hyperbaric pressures, large amount of nitrogen present in the air is absorbed in the blood of the attendants which may cause nitrogen narcosis. Sudden decompression releases the nitrogen in the form of bubbles in the blood stream and the tissues and this gives rise to a clinical syndrome termed 'bends' in the attendants and the patient. It is characterised by fatigue, transient visual disturbances and in more severe cases, by convulsions and shock. Aseptic bone necrosis and permanent neurologic deficit may occur occasionally as sequelae.

Therapeutic uses: Hyperbaric oxygen has a great therapeutic potential. The main handicaps in its use are the elaborate method of administration and the high risk of its toxicity and fire within the chamber. The main indications for its use are:

(a) **Respiratory disease of the newborn:** This condition is an example of the impairment of respiration at alveolar-capillary level. By nursing such babies in chambers pressurised to 2 to 4 atmosphere of absolute oxygen, a significant reduction in mortality has been achieved.

(b) **Carbon monoxide poisoning:** Use of hyperbaric oxygen has been found to maintain viability of hypoxic tissue despite the absence of sufficient amount of functioning hemoglobin in carbon monoxide poisoning. Increased tension of free oxygen speeds up the dissociation of carboxyhemoglobin into hemoglobin and increases the rate of pulmonary elimination of the poisonous gas. Carbon monoxide combined with myoglobin of the heart muscle is also rapidly split off, resulting in an improvement of the cardiac function.

(c) **Decompression sickness:** Hyperbaric oxygen dissolves the nitrogen bubbles and, therefore, can be used in the prevention of Caisson disease or bends during rapid decompression. More recently developed successful regimes combine hyperbaric pressures of 2 to 3 atmospheres with pure oxygen breathing.

(d) **Anaerobic infections:** Patients with gas gangrene due to *Cl. Welchii* may show marked improvement on exposure to hyperbaric oxygen at 3 atmospheric pressures. The duration of each exposure is 2 hours and 7 exposures may be given during a 3 day interval.

(e) **Aerobic infections:** Refractory chronic osteomyelitis with draining lesions, unresponsive to a combined medical and surgical treatment has been reported to heal on exposure to hyperbaric oxygen, along with the conventional treatment. The procedure may also prove useful for treatment of superficial burns infected with *Pseudomonas pyocyanea.*

(f) **Circulatory disturbances:** Hyperbaric oxygen has been used in a variety of circulatory disturbances including congenital cyanotic heart disease, cerebrovascular disease, acute myocardial infarction, peripheral vascular diseases, shock and cold injuries with variable results.

(g) **Surgery:** For open heart surgery of congenital cyanotic heart disease, for organ transplantation and for carotid endarterectomy, the use of hyperbaric oxygen has now been accepted. Ischemic skin grafts may survive more often if the patient is exposed frequently to oxygen at high pressures.

(h) **Malignancy:** Cells constituting a rapidly growing neoplasm are claimed to be hypoxic and consequently resistant to radiotherapy. Raising of oxygen tension in and around neoplasms by using hyperbaric oxygen is claimed to render them more sensitive to radiotherapy.

CARBON DIOXIDE: Carbon dioxide has marked effects on the central nervous system, the respiration and circulation. Normally it is produced in the body during tissue and food metabolism. The inspired atmospheric air contains 0.04 per cent of carbon dioxide.

Effects of carbon dioxide inhalation:

(a) *Respiration*: Carbon dioxide increases both the rate and the tidal volume of respiration. This effect is seen with inhalation of even 2 per cent carbon dioxide. Stimulation of respiration is achieved by its direct action on the brain stem areas (chemical drive), and to a much smaller extent by stimulation of the peripheral arterial chemoreceptors. The respiratory response to carbon dioxide is considerably enhanced when the PaO_2 is lowered.

(b) *Circulation*: Carbon dioxide, by a direct action, tends to decrease the heart rate and the myocardiac force of contraction. It also relaxes the vascular smooth muscle, tending to cause vasodilatation.

The direct circulatory effects are antagonised by the sympathetic activation induced by it, causing an increase in the peripheral release of the catecholamines. The total circulatory response, therefore, is the outcome of the two opposite actions. Thus, inhalation of carbon dioxide in a normal man increases the heart rate, the cardiac output, the systolic and the diastolic blood pressure and the pulse pressure. Cerebral and coronary vessels, which are devoid of a significant sympathetic control, dilate after carbon dioxide inhalation and so do the splanchnic and the skeletal muscle blood vessels. Carbon dioxide is probably the most potent cerebral vasodilator studied so far.

(c) *CNS*: Carbon dioxide, inhaled in low concentration, stimulates the cerebral cortex and reduces the electrical and the chemical seizure threshold. Higher concentrations depress the cortex, while activating the subcortical areas that have cortical projections.

Adverse reactions: Above a concentration of 7 per cent in inhaled air, carbon dioxide gives rise to headache, dizziness, mental confusion, palpitation, dyspnoea and an increase in blood pressure. Loss of consciousness occurs when the concentration of the gas exceeds 10 per cent. Withdrawal of carbon dioxide after prolonged inhalation often leads to pallor, hypotension, dizziness, nausea and vomiting. These effects can be minimised by tapered withdrawal of the gas. Carbon dioxide narcosis has already been discussed.

Preparations: (i) Carbon dioxide I.P. is marketed in steel cylinders painted grey, usually in a liquid form under a pressure of 58 to 72 atmospheres.

(ii) Combinations of oxygen and carbon dioxide in varying proportions are marketed as 'carbogen' cylinders. They usually contain 5 to 10 per cent of carbon dioxide, and the remainder is oxygen.

(iii) Solid carbon dioxide is available in two forms; dry ice and carbon dioxide snow. The latter is produced by evaporation of carbon dioxide under a pressure of 950 lbs. per square inch.

Therapeutic uses:

(1) **Respiratory depression:** Carbon dioxide, in the concentration of 5 to 10 per cent, has been used to stimulate respiration depressed by drugs, disease and injury. It must be pointed out, however, that carbon dioxide is potentially toxic, and itself capable of depressing the respiration. The patient, therefore, should be carefully watched and the gas should be discontinued if the patient fails to exhibit improvement. Assisted mechanical ventilation and administration of oxygen are generally more effective in combating respiratory depression.

(2) **Carbon monoxide poisoning:** Carbon dioxide, in the concentration of 5 per cent, is often used along with oxygen in this condition. It stimulates respiration, thus helping to wash out carbon monoxide and, in addition, reduces the blood pH, accelerating thereby the dissociation of carboxyhemoglobin to hemoglobin. Such therapy, however, may lead to a dangerous aggravation of the metabolic acidosis due to carbon monoxide poisoning.

(3) **Hiccup:** Inhalation of 10 to 25 per cent of carbon dioxide has been recommended in the treatment of intractable hiccup. It probably acts by virtue of its central depressant activity.

(4) **Neuropsychiatry:** Inhalation of 30 per cent of carbon dioxide with 70 per cent oxygen has been employed in psychiatry for the treatment of anxiety neurosis and personality maladjustments. It causes a loss of consciousness and convulsions may appear in some cases. The procedure is empirical and its therapeutic value is not well established.

(5) **Local uses:** Carbon dioxide snow, which has a temperature of —80°C, has a destructive action on tissues and is used to destroy warts and naevi by local application for 5 to 6 seconds. The procedure is almost painless and scarring is minimum. The surrounding tissue should be covered with soft paraffin for protection.

(6) **Miscellaneous:** Carbon dioxide has been used to increase the speed of induction and emergence from anaesthesia. It has also been recommended for prevention of postoperative atelectasis. Carbon dioxide inhalation rapidly terminates petit mal seizures, while hyperventilation elicits the characteristic EEG pattern of petit mal epilepsy. The gas is also useful for studying the mechanisms controlling respiration and cerebral blood flow.

Supersaturated solution of carbon dioxide or aerated waters possess a mild rubefacient action and are believed to increase the secretion of gastric juice particularly hydrochloric acid. They are often used as carminatives and for masking unpleasant taste of saline purgatives.

HELIUM: This inert gas, in the concentration of 80 per cent along with 20 per cent oxygen, is used by intermittent inhalation for treating prolonged asthmatic attacks resistant to other forms of therapy. Because of its lower density, it minimises the breathing effort. It is also employed prophylactically for prevention of Caisson disease, and in the treatment of edema and spasm, of larynx. It also serves as a useful, non-inflammable diluent for oxygen during anaesthesia and open heart surgery. The gas is costly.

TREATMENT OF CYANIDE POISONING

Cyanide is one of the deadliest of all poisons causing death within a matter of few minutes. It acts by forming a complex with cytochrome oxidase, thereby inhibiting cellular respiration. Cyanide normally present in the body is biotransformed to the much less toxic thiocyanate; this reaction is catalysed by an intracellular enzyme *rhodonase* which requires thiosulfate or colloidal sulfur as a substrate. As the availability of this substrate is essentially limited, rhodonase is unable to biotransform large amounts of cyanide.

In the treatment of cyanide poisoning, initially methemoglobinemia is produced by amyl nitrite inhalations given for 30 seconds every 2 minutes along with intravenous administration of 300 to 500 mg. of sodium nitrite dissolved in 10 to 15 ml. of water. Methemoglobin competes with cytochrome C oxidase for cyanide, resulting in the formation of cyanmethemoglobin and thus protects the enzyme. This is followed by administration of sodium thiosulfate slowly, intravenously, in the dose of 12.5 g. in a total volume of 50 ml. The injection is given over a period of 10 minutes. This results in the formation of relatively non-toxic thiocyanate which is excreted in urine.

It must be emphasised that the treatment must be instituted immediately to prevent the fatal outcome. Hyperbaric oxygen and intravenous methylene blue as 1 per cent solution in the dose of 1 to 4 mg. per kg. are the other measures employed.

68 Enzymes in Therapy

Enzymes being extremely potent substances, the possibility of their therapeutic application is attractive. However, majority of these substances have to be administered parenterally as they are inactivated within the gastrointestinal tract. In addition, because of their proteinic nature, they are likely to evoke allergic manifestations and because of their high potency, their careless use may result in alarming adverse effects. Lastly, because of the highly complicated method of their preparation, the cost of such therapy is likely to be high.

Enzymes such as pancreatin, diastase, pepsin and papain, used in the treatment of certain gastrointestinal disturbances have been discussed in Chapter 35. The enzymes fibrinolysin, thromboplastin, urokinase and arvin involved in the process of blood coagulation are discussed in Chapter 29. The therapeutic application of penicillinase and pancreatic dornase is discussed in Chapters 41 and 22 respectively. Use of asparaginase is discussed in Chapter 55.

The other enzymes used therapeutically are:

HYALURONIDASE (Hyalase, Rondase): This enzyme, prepared from mammalian testes acts by de-polymerizing hyaluronic acid, an essential component of the intercellular ground substance which determines the permeability of the tissue. Thus, hyaluronidase, administered subcutaneously, increases the tissue permeability or exhibits 'spreading activity'. Certain snake-venoms and bee-venoms also contain hyaluronidase. Similarly, certain virulent organisms also liberate hyaluronidase.

Hyaluronidase B.P. is an odourless, fluffy powder containing not less than 300 units of activity per mg. Therapeutically, hyaluronidase is employed to promote the rapid absorption of drugs and fluids given subcutaneously or intramuscularly. The agent is particularly useful in aiding the absorption of relatively large quantities of fluids, administered subcutaneously in infants and young children, in whom intravenous injection may be difficult. The subcutaneous injection of 500 to 1000 units of the enzyme at the site of fluid infusion enables its subcutaneous administration at the rate of 10 ml. per minute.

Substances used in radiography are rapidly absorbed on intramuscular injection with the aid of hyaluronidase, thus providing an alternative to their intravenous administration. The agent has also been used to promote the absorption of blood and fluid in traumatic or post-operative edema or hematoma, and along with local anaesthetics.

Hyaluronidase is antigenic and may occasionally produce allergic reactions. Because of the danger of spreading the infection, the enzyme should not be injected into or around an infected area. Malignancy is also considered a contraindication for hyaluronidase for similar reasons.

STREPTOKINASE AND STREPTODORNASE: Streptokinase, an enzyme produced by certain strains of beta hemolytic streptococci, causes fibrinolysis and dissolution of clot mainly by converting the intrinsic plasminogen present in the fibrin clot to its active form plasmin. In addition, it is also capable of activating the plasminogen in the body fluids (extrinsic plasminogen) to plasmin, but this mechanism is probably of secondary importance in its clot-dissolving effect. The enzyme has its maximum activity between pH 7.3 to 7.6.

Streptodornase is not a single enzyme but a group of rapidly acting enzymes which promote the depolymerization of the complex nucleoproteins derived from degenerated leucocytes and injured tissue cells. They act directly and not through plasminogen activation. Their action results in a rapid conversion of thick, viscous and purulent material to thin, easy flowing fluid. The enzymes do not attack the nucleoproteins of living cells. Their optimum activity is observed between the pH 7.0 and 8.5 and requires the presence of magnesium ions.

Both these enzymes are stable for several months in desiccated form but solutions at room temperature deteriorate rapidly.

Adverse reactions: As with other enzymes, the use of streptokinase-streptodornase may occasionally result in allergic reactions like urticaria, rash, fever and anaphylaxis. A febrile reaction may occur on topical administration, but can be minimised by frequent drainage. Pain and irritation may follow intramuscular and buccal administration. Streptokinase-streptodornase should not be employed in the presence of acute cellulitis and inflammation, as it may encourage the spread of localised infection. Where bronchopleural fistulas have previously existed, there is a danger of their reopening, especially in active tuberculosis. Injection of the enzymes into the cavity after operation to prevent adhesions may result in hemorrhage from the sutured wound. These enzymes are contraindicated in the presence of active hemorrhage and in those with low fibrinogen levels. Since these enzymes are bacterial antigens, therapy with them results in rapid antibody formation rendering further treatment ineffective.

Preparations: Streptokinase and streptodornase (Varidase) are marketed as a dry, sterile powder for topical application containing 100,000 units of streptokinase and 25,000 units of streptodornase, buffered with sodium phosphate to a pH of 7.5. A jelly containing an equivalent amount of the enzymes in 15 ml. is also available. The powder available for injection contains 20,000 units of streptokinase with 5,000 units of streptodornase per vial, while buccal tablets contain 10,000 units of streptokinase and 2,500 units of streptodornase.

Therapeutic uses: Streptokinase-streptodornase is used topically or by instillation into closed body cavities to liquefy clotted blood or fibrinous or purulent material. The main indication for its use is as an adjunct in the treatment of hemothorax, hematoma, empyema and suppurative lesions. For this purpose, a solution containing 200,000 units of streptokinase and 50,000 units of streptodornase in 10 ml. of isotonic saline is suggested for large cavities such as the pleura, and 10,000 units of streptokinase and 2,500 units of streptodornase in 2 to 3 ml. of isotonic saline for small cavities, as in the treatment of maxillary sinus empyema. The instillation may be repeated depending upon the quantity and the character of the fluid aspirated. Antibiotics may also be instilled along with the enzymes. The fibrinolytic activity starts within 45 to 60 minutes after instillation, reaches peak by 12 to 24 hours and is dissipated within 24 to 48 hours. The enzyme has recently been used in pulmonary thrombosis. Streptokinase has been used by slow intravenous infusion as a thrombolytic agent.

The enzymes have also been employed locally as wet dressings for debridement in the treatment of chronic suppurations.

TRYPSIN: This enzyme is obtained from an extract of the ox pancreas. It is available as a white powder soluble in water. The enzyme is active at a pH range of 5 to 8 with optimum activity at the pH 7.

Trypsin directly hydrolyzes natural proteins, including the respiratory mucins. Unlike streptokinase, it does not require a cofactor for this effect.

The adverse effects of trypsin are similar to those of streptokinase-streptodornase. Application of the dry powder to surface lesions may cause a severe burning sensation. Intramuscular injection may be followed by pain and induration at the site of injection and occasionally by fever, leucocytosis, angio-neurotic edema and urticaria.

Contraindications and precautions for the use of trypsin are similar to those with streptokinase-streptodornase. The agent should be used cautiously in the presence of renal damage and be avoided in individuals with hepatic insufficiency. It should never be given intravenously.

Trypsin has therapeutic applications similar to streptokinase-streptodornase. For infiltration or by instillation, it is used as a solution containing 3 to 5 mg. of the enzyme per ml. The dry powder may be applied every 15 to 30 minutes to small areas and every 3 hours to large areas; wet dressings and irrigations should be repeated 3 hourly. Small gelatin capsules containing the enzyme may be inserted into inirrigable sinuses and fistulae. An aerosol of trypsin has been used to liquefy excessive bronchial secretions but its irritant nature makes it of doubtful value.

CHYMOTRYPSIN: This is a proteolytic enzyme obtained from the bovine pancreas. It is available as tablets containing 50,000 units of the enzyme per tablet. Tablets containing trypsin and chymotrypsin are also available.

Chymotrypsin is proposed for use as an adjunct to the conventional treatment of traumatically induced inflammation and edema of soft tissues. It is applied locally or given orally. However, its usefulness is doubtful. Its oral toxicity is mild.

ALPHA-CHYMOTRYPSIN: This proteolytic enzyme is mainly used in ophthalmology for dissolving the suspensory ligament of the lens which facilitates the dissection of the lens during intracapsular extraction of cataract. The procedure is called zonulolysis. It is used as 0.2 to 0.5 ml. of a freshly prepared 1 : 5000 solution injected slowly behind the lens into the posterior chamber. The adverse effects include transient glaucoma, wound disruption, loss of vitreous and rarely retinal damage, if it penetrates the vitreous. It can also be applied locally.

Proteolytic enzymes from carica papaya (Papase) and concentrated protease (bromelains) obtained from pineapple plant have the same indications as trypsin. They act by depolymerizing the soft fibrin deposits in the inflamed areas and by facilitating the drainage of fluids. Their therapeutic use is not well established.

69 Vitamins

A vitamin is an exogenous substance essential in very small amounts for the various metabolic functions of the body. Some of the vitamins such as vitamin K, pantothenic acid, folic acid, cyanocobalamin are also synthesized by the intestinal bacterial flora. Vitamins form components of important enzyme systems which catalyse the reactions by which the body metabolizes carbohydrates, proteins and fats. It is beyond the scope of this book to discuss in detail the physiological aspects of vitamins. The discussion is, therefore, limited to the pharmacological aspects, when vitamins are employed as drugs for therapeutic purposes.

A normal individual ingesting a well balanced diet gets adequate supply of these vitamins and needs no supplement. Vitamin deficiency, however, can occur in various ways:

I. **Poor dietary intake:** Undernutrition as is prevalent in the economically developing countries and also in persons who, for any reason, are not eating properly.

II. **Inadequate absorption from the gastrointestinal tract:** Chronic diarrhoea, malabsorption syndrome, obstructive jaundice, interference with the function of the intestinal flora by oral antibiotics, interference with absorption by drugs like liquid paraffin.

III. **Interference with utilization:** Usually by drugs e.g. diphenylhydantoin interferes with folic acid utilization; INH prevents the conversion of pyridoxal to pyridoxal phosphate.

IV. **Increased demand:** During growth, in pregnancy, during lactation, under stress, in fevers and other catabolic conditions such as hyperthyroidism.

Vitamins are usually classified as (a) fat soluble vitamins such as Vit. A, D, E and K and (b) water soluble vitamins such as B. complex and C. The former can be stored in the body considerably and hence, excessive administration of these can cause serious toxicity. Water soluble vitamins, on the other hand, are rapidly excreted in the urine following excessive administration and tend to have low toxicity.

FAT SOLUBLE VITAMINS

VITAMIN A: Vitamin A, a complex primary alcohol, is obtained from the diet and also by conversion of the plant pigment called carotene. Carotene exists in 3 isomeric forms, alpha, beta and gamma. The beta isomer occurs most abundantly in nature and is postulated to give rise to one or two molecules of vitamin A by biotransformation in the body.

Sources: Carotene is present in several green vegetables, notably in carrots, spinach and watercress and is also found in egg yolk, milk, butter, whole wheat, cheese and tomatoes. Animal sources such as the cod, the halibut and the mammalian liver contain large amounts of vitamin A. The daily requirement of vitamin A is about 5000 U. in adults and older children and about 3000 U. in children below 5 years.

Vitamin A and the carotenes are stable to heat in the absence of oxidising agents, and the ordinary cooking processes do not destroy the vitamin A activity of the vegetables. Exposure to light and rancidity of fat hasten vitamin A destruction but frozen foods retain their vitamin A content for a sufficiently long time. The daily requirements in terms of units should be doubled if the vitamin is given in the form of beta carotene, as the utilization of the latter is not as efficient as that of vitamin A.

Physiological functions: Vitamin A plays a vital role in the phenomenon of dark adaptation where it is essential for the synthesis of rhodopsin, the photosensitive pigment of rods. The latter decomposes when light strikes the rod, thus initiating the nerve impulse. The vitamin is also essential for the integrity of epithelial cells, for the synthesis of glucocorticoids and cholesterol, and for somatic growth.

Clinical vitamin A deficiency is characterized in early stages by night blindness, xerosis of conjunctivae (manifested as Bitot's spots) and xeropthalmic or "dry eye". This may be associated with squamous metaplasia of the mucosal surface of the upper respiratory tract and the periodontal tissues, follicular hyperkeratosis of the skin (also termed toad skin), and an increased incidence of renal calculi. Similar changes may occur in the intestinal epithelium leading to diarrhoea. In advanced stages, true keratomalacia may occur, leading to blindness. The manifestations of this condition are necrosis, ulceration and finally, perforation of the cornea and panopthalmitis.

Absorption, fate and excretion: Vitamin A is readily absorbed from the gastrointestinal tract. The absorption is reduced in the presence of biliary obstruction or liver disease; however, this is not due to bile deficiency as externally administered bile salts are unable to promote the absorption of vitamin A. It is likely that specialised enzymatic processes concerned with intestinal absorption of the vitamin from the small intestine are deficient in hepatic insufficiency.

Following oral administration, plasma peak levels are reached within 4 hours. It is stored in the Kupffer cells of the liver and following hepatic saturation, it is released into the plasma in small amounts. Liver disease, therefore, may be associated with low plasma vitamin A levels. In the plasma, vitamin A is mainly present as alcohol and is transported in combination with globulin. In kwashiorkor, plasma vitamin A levels are low, probably owing to the deficiency of the carrier protein.

As opposed to vitamin A, carotene is absorbed slowly from the intestines and absorption requires the presence of bile and absorbable fat in the intestinal tract. Carotene is converted to vitamin A in the intestinal wall and is subsequently stored in the liver. In the event of large dietary intake of carotene, some of it may escape into the circulation, leading to carotenemia, which causes a characteristic yellow discoloration of the skin.

Vitamin A is extensively metabolised in the body; conversion to carbon dioxide and fatty acids and water soluble metabolites has been reported. Normal human urine does not contain any vitamin A.

Adverse reactions: Both acute and chronic intoxication with vitamin A have been reported. Thus, consumption of the liver of polar bear (vitamin A content, 10,000 to 34,000 I.U./g.) leads to anorexia, nausea, vomiting, abdominal pain, headache, papilloedema, diplopia, convulsions, delirium and coma. Several of these effects are similar to those of a brain tumour. Bulging of fontanelles and vomiting have also been reported in infants given a single, large dose of 300,000 I.U. of vitamin A.

Chronic intoxication usually develops following the administration of large doses of vitamin A (over 300,000 units daily) for prolonged periods. The usual symptoms are anorexia, dry itching skin (hyperkeratosis), loss of weight, increased irritability, low grade fever, alopecia, dependent edema with erythema and ecchymosis, bleeding, fissuring, refractory skin ulcers, anemia and hepatosplenomegaly. Headache and visual upsets are often encountered. Subcutaneous swellings, tenderness over long bones and bony exostoses are other notable features. X-ray studies have revealed premature closure of epiphyses and consequent retardation of growth in children. The symptoms usually appear after a latent period of 6 to 15 months. The characteristic skin desquamation is a major diagnostic point of hypervitaminosis A.

Bioassay: Vitamin A is bioassayed by its ability to stimulate growth in rats suffering from experimental vitamin A deficiency. One unit of vitamin A is equivalent to 0.344 μg of the standard preparation.

Preparations and dosage: These are:

(i) Concentrated vitamin A solution I.P. is a pale yellow, oily liquid with a slightly fishy odour. It contains not less than 50,000 units/ml. of vitamin A activity. Dose: 0.06 to 0.6 ml.

(ii) Vitamin A tablet strong N.F.: Contains 50,000 units of vitamin A. Dose: 1 to 2 tablets daily.

(iii) Vitamin A injection N.F.: Contains 100,000 units per ml. Dose: 1 ml. I.M. once or twice a week.

Synthetic and natural preparations containing both vitamin A and vitamin D are also available. These are:

(i) Concentrated vitamins A and D solution: Contains not less than 5,000 units of antirachitic activity (vitamin D). Dose: 0.06 to 0.6 ml. daily.

(ii) Vitamins A and D capsule I.P. or tablet N.F.: Contains not less than 6,000 units of vitamin A and not less than 1,000 units of antirachitic activity. Dose: 1-2 capsules daily.

(iii) Vitamins A and D (oily) injection N.F.: Contains 60,000 units of vitamin A and 10,000 units of vitamin D per ml. Dose: 1 ml. once or twice a week I.M.

(iv) Shark liver oil I.P. is obtained from the fresh or carefully preserved livers of the shark and allied species. It contains not less than 6,000 units of vitamin A activity in 1 g. Dose: 0.2 to 1 ml. by mouth, approximately equivalent to 1,500 to 7,500 units of vitamin A.

(v) Dilute shark liver oil I.P. is prepared by the addition of decolorised, deodorised arachis oil to shark liver oil and fortifying it with vitamin D. It contains not less than 1,000 units of vitamin A activity and not less than 100 units of antirachitic activity per g. Dose: 4 to 12 ml. daily by mouth in divided portions.

(vi) Halibut liver oil is extracted from the fresh or suitably preserved liver of halibut species belonging to the genus *Hippoglosus*. It contains not less than 30,000 units of vitamin A activity and 2,500 to 3,500 units of antirachitic activity per g. Dose: 0.2 to 0.5 ml. daily.

Therapeutic uses: In the treatment of nightblindness and xeropthalmia, vitamin A is administered in the dose of 50,000 to 75,000 units, usually in the form of halibut liver oil. This condition rarely responds completely to vitamin A therapy except in the early stages. Severe cases may need parenteral therapy. Improvement begins within a week after vitamin administration but several months may be required for complete healing. Hence, vitamin A should be used more for prevention than for treatment. This is especially important in countries where undernutrition is common.

Deficiency of vitamin A is also seen in coeliac disease, sprue, and with excessive use of liquid paraffin. This generally responds to the treatment outlined above.

Vitamin A has been used empirically to increase host resistance in infections like common cold and influenza, and to promote growth in children, in degenerative conditions of the central nervous system and in a variety of skin disorders like sunburn and acne vulgaris. None of these conditions, however, is benefited by such therapy.

VITAMIN D: See Chapter 64.

VITAMIN E (Alpha tocopherol): This vitamin is present in soya bean oil, wheat germ oil, rice germ oil and in green leaves of lettuce. In lower animals such as rats, its prolonged deprivation leads to sterility in male and abortion and foetal resorption in the female. In guineapigs, vitamin E deficiency gives rise to dystrophy of cardiac and skeletal muscle. There is some evidence that human megaloblastic anemia resistant to both vitamins B_{12} and folic acid may respond to large doses of vitamin E. However, deficiency syndrome due to vitamin E lack in humans is not established.

Vitamin E is bioassayed by its ability to protect the foetuses of pregnant rat when the animal is deprived of dietary vitamin E.

Vitamin E has been used empirically in a variety of disorders ranging from sterility to myopathies. Because of the uncertainty regarding its physiological function, no definite indication for its use exists at present.

VITAMIN K: See Chapter 29.

WATER SOLUBLE VITAMINS

Vitamin B Complex group includes thiamine, riboflavine, nicotinic acid, pyridoxine, pantothenic acid, inositol, biotin, methionine, folic acid and cyanocobalamin.

THIAMINE (Aneurine, vitamin B_1): This was the first member of the B complex series identified chemically, and hence the designation, vitamin B_1. It can withstand boiling but is easily destroyed by an alkaline solution. Peas, beans, oatmeal, the outer germ layer of the cereal grains, peanuts and mammalian organ meat are rich sources of thiamine. In addition, appreciable amounts are also present in vegetables and fruits.

Physiological function: Thiamine pyrophosphate, the physiologically active form of vitamin, constitutes the prosthetic group of the decarboxylases involved in the metabolism of pyruvic and alpha-ketoglutaric acids and thus plays an important role in the intermediary carbohydrate metabolism.

Thiamine deficiency produces a symptom complex with characteristic neuropathy termed *beriberi.* Beriberi occurs in three main forms: *wet beriberi,* characterised by dependent edema and high output cardiac failure; *infantile beriberi* which occurs within the first few months of life, with a high output failure, cyanosis, tachycardia, convulsions, anorexia, vomiting, greenish stools and sometimes sudden death as the noteworthy features; and *dry beriberi,* which is usually seen in adults and in which peripheral neuritis and muscular atrophy are predominant. Even though neuropathy in some form is common to all the three varieties, it is the most important manifestation in dry beriberi, while nervousness, increased irritability and depression may occur in all the three types.

In addition to beriberi, *Wernicke's encephalopathy,* characterised by confusion, ophthalmoplegia, nystagmus, tremors and often peripheral neuropathy, is looked upon as a manifestation of severe thiamine deficiency; Korsakoff's psychosis encountered in chronic alcoholics may owe some of its symptoms to the lack of this vitamin and so may the neuritis encountered in pregnancy and pellagra.

Vague symptoms like epigastric pain, anorexia, flatulence, constipation and lethargy or easy fatiguability are also attributed to thiamine deficiency.

Absorption, fate and excretion: The daily thiamine requirement is believed to be between 1 to 2 mg.

Thiamine is incompletely absorbed from the gastrointestinal tract mainly from the duodenum and the small intestine. It is distributed in all tissues. Approximately 1 mg. of the vitamin is degraded in the tissues per day. Thiamine appears in urine only when the minimal requirements are satisfied and the stores (liver, heart, brain, kidney) are saturated.

Adverse reactions: Thiamine administered orally usually does not evoke any adverse effects. Administration of large doses by intramuscular or intravenous route, however, may result in anaphylactic shock. Large doses may also interfere with the metabolism of other members of B complex group. Except in the initial treatment of acute wet beriberi, there is no justification for exceeding the dose of 100 mg. daily, parenterally.

Preparations and dosage:

(i) Thiamine hydrochloride tablet I.P. contains 5 to 50 mg. of the drug. Dose: prophylactic, 2 to 5 mg. daily; therapeutic 25 to 100 mg. daily.

(ii) Thiamine hydrochloride injection I.P. contains 25 mg. of the vitamin per ml. Dose: 25-100 mg. S.C. or I.M.

Therapeutic uses: Thiamine deficiency can be prevented by improvement in the dietary intake and by preventing overmilling of cereals, particularly rice. Acute wet beriberi responds dramatically to oral or parenteral administration of thiamine. Treatment is usually initiated with 10 to 30 mg. of thiamine, given parenterally. A maintenance dose of 5 to 10 mg. is given subsequently by mouth. Within a few hours of thiamine therapy, diuresis starts and most of the edema fluid is eliminated within 48 to 72 hours.

In dry beriberi, it is probably advisable to use thiamine with other members of vitamin B complex group. Alcoholic and pregnancy neuritis respond well to the oral administration of 5 to 10 mg. of thiamine daily. In Wernicke's encephalopathy, a dose of 50 mg. is usually advocated; improvement is rapid, particularly in opthalmoplegia. In contrast, the neuritis of Korsakoff's psychosis may respond slowly or not at all.

RIBOFLAVINE (Vitamin B_2): Riboflavine occurs as yellow or orange yellow crystals; it is heat stable.

Sources: These include liver, kidney, meat, eggs, milk, yeast and green vegetables. In plants, it is present as a greenish flourescent pigment. The daily riboflavine requirement for an adult is 1.5 to 3 mg. while a child requires 0.6 to 2 mg. per day.

Physiological functions: The physiologically active form of riboflavine is formed by phosphorylation. The two coenzymes flavin mononucleotide (FMN) and flavine adenine dinucleotide (FAD), which contain this active form, play an important role in transfer of hydrogen and in oxidation of carbohydrates, amino acids and other products of metabolism.

Riboflavine deficiency in man results in a syndrome characterised by angular stomatitis, glossitis and a peculiar magenta pigmentation of the tongue, cheilosis (loss of epithelium at the mucocutaneous junction of lips) resulting in reddened, shiny and denuded lips, seborrheic follicular keratosis of the nasolabial folds, nose and forehead, dermatitis of the ano-genital region and 'burning feet'. Certain ocular manifestations such as conjunctivitis, blepharospasm, photophobia, burning, lacrimation and vascularization of the cornea leading to diminution in visual acuity, are seen in a large proportion of cases.

Absorption, fate and excretion: Riboflavine is synthesized in the large intestine, but whether it is available for absorption is uncertain.

Riboflavine and FMN are readily absorbed from the gastrointestinal tract. Phosphorylation of riboflavine to the active form occurs in the intestinal wall, liver and erythrocytes. Excess of vitamin B_2 is stored in liver and kidneys. Only 9 per cent of the orally administered dose appears in urine; the metabolic fate of the remainder is not known. Riboflavine, administered by oral or parenteral route, does not produce any significant toxic effects. Excess of riboflavine may impart fluorescence to the urine during its excretion.

Preparations and dosage:

(i) Riboflavine tablet I.P. contains 2 mg. of the vitamin. Dose: prophylactic, 1 to 4 mg. daily; therapeutic, 5 to 10 mg. daily.

(ii) Riboflavine injection I.P. contains 10 mg. of riboflavine per ml. Dose: 2-5 mg. daily S.C. or I.M.

Therapeutic uses: In the treatment of ariboflavinosis, the vitamin is given daily in the dose of 2 to 10 mg. It is usually employed along with other members of vitamin B group.

NICOTINIC ACID AND NICOTINAMIDE: This vitamin, also termed as *pellagra preventing factor* (PPF), is a simple organic acid. Its amide, nicotinamide, is also equally effective in the treatment of pellagra. Nicotinic acid is present in large quantities in rice polishings, liver, milk, eggs and lean meat, and to a smaller extent in potatoes and in vegetables. The vitamin is also synthesized from tryptophan in the intestines and in tissues. The normal daily requirement of nicotinic acid is between 15 and 20 mg.

Physiological functions and pharmacolo-

gical actions: (a) Nicotinic acid as nicotinamide adenine dinucleotide (NAD) and its phosphate (NADP) is the constituent of a number of coenzymes involved in the metabolism of proteins necessary for cellular respiration.

Pellagra, a symptom complex secondary to deficiency of nicotinic acid, occurs, endemically in individuals subsisting mainly on a diet of maize. The latter has a poor nicotinic acid and tryptophan content. Non-endemic pellagra occurs in chronic alcoholism, and in various malabsorption syndromes, in carcinoid syndrome, in liver cirrhosis, with poorly controlled diabetes mellitus, and in cachexia secondary to malignancy.

The characteristic features of pellagra are dermatitis and pigmentation of the skin, especially in regions exposed to sunlight and at various pressure points, anorexia, lethargy, stomatitis, glossitis, diarrhoea, mental confusion (dementia) and a megaloblastic anemia. Hallucinations and other mental abnormalities may occur and spinal cord degeneration leading to spastic paraplegia occasionally develops as a complication.

Though nicotinic acid deficiency is the major cause of pellagra, recent evidence indicates that folic acid deficiency is probably responsible for the megaloblastic anemia, and deficiency of riboflavine which is necessary for the conversion of tryptophan into nicotinic acid, and of pyridoxine may account for the cheilosis, stomatitis, dermatitis, vaginitis and proctitis.

(b) Nicotinic acid, on oral or parenteral administration, causes peripheral vasodilatation by direct relaxation of the vascular smooth muscle and causes flushing. This may be accompanied by urticaria and pruritus. Large doses of nicotinic acid lower the serum cholesterol levels and activate fibrinolysis. Nicotinamide is devoid of these effects.

Absorption, fate and excretion: Both nicotinic acid and nicotinamide are readily absorbed from the gastrointestinal tract and from parenteral sites. They are distributed to all the tissues. Inactivation occurs mainly by N-methylation and to some extent by conjugation, and the products are eliminated in urine. The vitamin may appear in urine in the active form if large doses are given by mouth.

Adverse reactions: Besides flushing, urticaria and pruritus which occur on oral or parenteral administration of nicotinic acid, large doses of the vitamin may cause furunculosis and other skin lesions, malaise, gastrointestinal disturbances, activation of peptic ulcer, bilateral amblyopia, jaundice and impairment of liver function, decrease in glucose tolerance and hyperuricemia. Most of these effects regress on stopping the drug. Nicotinic acid has been reported to potentiate the action of phenothiazines and hypotensive agents.

Preparations and dosage:

(i) Nicotinic acid tablet I.P. contains 50 mg. of the vitamin. Dose: prophylactic 15 to 30 mg. daily; therapeutic, 50 to 250 mg. daily.

(ii) Nicotinic acid injection is available in 10 ml. ampoules containing 100 mg. of the vitamin.

(iii) Nicotinamide tablet I.P. contains 50 mg. of the drug. Dose: similar to nicotinic acid.

(iv) Nicotinamide injection I.P. contains 50 mg. of nicotinamide per ml. It is usually administered intravenously in the daily dose of 50 to 250 mg.

Therapeutic uses: (a) *Pellagra*: Nicotinic acid or its amide is used in the treatment of pellagra in the daily dose of 50 to 500 mg. Usually, nicotinamide is preferred because of its lack of side effects. If the patient is unable to accept oral medication, nicotinamide may be administered parenterally. Therapy with the vitamin produces a striking improvement in the mental, dermal and alimentary manifestations within 24 hours. The neuropathy and the lesions of face and lips, however, may need adjuvant treatment with riboflavine.

(b) *Miscellaneous*: Nicotinic acid, in the dose of 100 to 300 mg. by subcutaneous or oral route, has been employed as a vasodilator in the treatment of Meniere's disease and in peripheral vascular disorders including chilblains and frostbite. Large doses of the vitamin (3 to 6 g. daily) have been given orally to reduce serum cholesterol levels.

PYRIDOXINE (Vitamin B_6): Pyridoxine, pyridoxal and pyridoxamine are collectively called as vitamin B_6. It is present in yeast, cereals, legumes, milk, meat etc. All the three forms are converted in the body to pyridoxal phosphate which is probably the active physiological form. The daily requirement is estimated at 1-2 mg.

Physiological functions: Pyridoxal phosphate acts as a coenzyme for amino acid decarboxylases and transaminases. It is thus intimately involved in the synthesis and degradation of biogenic amines like the catecholamines, 5-hydroxytryptamine and other important compounds like gamma-amino butyric acid. Vitamin B_6 deficiency may cause derangement of enzymes controlling carbohydrate metabolism resulting into abnormal G.T.T.

A syndrome in infants secondary to ingestion of a proprietary milk preparation deficient in pyridoxine has been described. The characteristic features include irritability, abdominal distension, twitching, failure to gain weight, hypochromic microcytic anemia and convulsions. The anemia is probably due to inadequate utilization of iron for erythropoiesis. Pyridoxine deficiency in adults may lead to lesions of the skin and mouth resembling those seen in ariboflavinosis and pellagra, to peripheral neuritis and to mental changes. Convulsions and hypochromic microcytic anemia have also been observed.

Absorption, fate and excretion: All the three forms of the vitamin are readily absorbed from the gastrointestinal tract. The end product of metabolism is 4-pyridoxic acid, which is eliminated in urine. Pyridoxine, administered in physiological doses does not produce any untoward effects. Very large doses, however, may lead to convulsions.

(i) Pyridoxine tablet I.P. contains 5 mg. of the drug. Dose: 5 to 10 mg. daily.

(ii) Pyridoxine injection N.F. contains 25 mg. of the hydrochloride salt per ml. Dose: 25-100 mg. I.M. or I.V.

Therapeutic uses: In the treatment of convulsions due to pyridoxine deficiency in infants, the vitamin is administered parenterally in the dose of 4 mg. per kg. daily for short periods. Anemia secondary to pyridoxine deficiency usually responds to 50 to 150 mg. of the vitamin daily in divided doses. Pyridoxine is also used as an adjuvant in the dose of 5 to 10 mg. in the treatment of pellagra.

Pyridoxine, in the daily dose of 20 to 100 mg., has been employed in vomiting of pregnancy and in radiation sickness. It has also been tried empirically in muscular dystrophies and in Raynaud's disease without conclusive benefits.

The peripheral neuritis following isonicotinic acid hydrazide, optic neuritis following penicillamine and alcoholic neuritis respond to pyridoxine therapy. Abnormal G.T.T. following oral contraceptives may also respond to pyridoxine.

PANTOTHENIC ACID (Vitamin B_3): This is an organic acid which serves its physiological function by being converted into coenzyme A. Yeast, wheat, peanuts, cereals, milk and liver contain large amounts of pantothenic acid. The daily human requirement of pantothenic acid is estimated to be below 5 mg.

Physiological actions: Coenzyme A is involved in several fundamental biological reactions. In general, all the acetylation reactions are greatly influenced by this enzyme.

Pantothenic acid deficiency in human beings under normal circumstances is not known. In animals, deficiency of the vitamin results in keratitis, dermatitis, arrest of growth, depigmentation of hair, neuromuscular degeneration and fatal bilateral adrenal hemorrhage. Artificial deficiency produced in human volunteers by administration of a low vitamin diet containing a pantothenic acid antagonist is characterised by fatigue, malaise, headache, somnolence, paraesthesiae, nausea, occasional vomiting, abdominal cramps and flatulence.

Absorption, fate and excretion: The vitamin remains stable in foodstuffs for long periods and little is destroyed during cooking.

Pantothenic acid is rapidly absorbed from the gastrointestinal tract and is concentrated in liver, heart and kidneys. It is mainly excreted in the urine.

Pantothenic acid is non-toxic and does not possess any other known pharmacological actions.

Preparations and dosage:

(i) Calcium pantothenate: This is the calcium salt of pantothenic acid. It is available in 10 mg. tablets. Dose: 10 to 50 mg.

(ii) Dexpanthenol: This is an alcoholic analogue of pantothenic acid which is readily converted to the parent compound on administration. It is administered by I.M. or I.V. injection in the dose of 250 to 500 mg. For topical application, 2 to 5% creams and ointments are available.

Therapeutic uses: Calcium pantothenate has been employed in a variety of conditions including streptomycin toxicity, post-operative paralytic ileus, rheumatoid arthritis and as a nutritional supplement along with other members of the B-complex group. Dexpanthenol has been employed systemically for the prevention and treatment of post-operative intestinal atony and topically for various skin lesions including burns, wounds and ulcers. The utility of both calcium pantothenate and dexpanthenol in these conditions, however, appears equivocal.

BIOTIN: Biotin is an organic acid which functions as a coenzyme for numerous carboxylation reactions. Biotin deficiency is not encountered naturally in humans but has been produced in human volunteers by administering a diet containing large amounts of raw egg white or avidin. It is characterised by seborrheic dermatitis, lassitude, anorexia and paraesthesiae. The daily human requirement of the vitamin is unknown. The vitamin is synthesized by the intestinal flora. As a clinical deficiency syndrome has not been demonstrated clearly so far, the vitamin does not have any therapeutic application.

Miscellaneous: These include inositol, choline, methionine and para-aminobenzoic acid (PABA). Choline and methionine, the so called "lipotropic factors", have been used in the treatment of liver cirrhosis; inositol has been used in the management of diseases associated with the metabolism of fat. This is based on the observation that experimental deficiency of these in animals causes fatty livers. Their efficacy in human conditions is, however, equivocal. The serious side effects of PABA include toxic hepatitis, hypoglycemia, crystalluria, leucopenia and agranulocytosis.

ASCORBIC ACID (Vitamin C): The dietary sources of ascorbic acid include citrus fruits, tomatoes, plants, potatoes and green vegetables. One ml. of lemon juice contains about 0.5 mg. of this vitamin. Lemon juice as a sole source of this vitamin is not reliable and was the cause of outbreak of scurvy in the North Pole Expedition of 1875. Although cereals and other seeds are devoid of vitamin C, produce it on germinating. Levo compound is more active. Vitamin C is unstable and is destroyed by boiling and by alkali.

Physiological actions: Ascorbic acid, along with its oxidation product dehydroascorbic acid, is intimately involved in biological oxidation and reduction reactions and in cellular respiration. Ascorbic acid is essential for the functional integrity of sulfhydryl group of enzymes and also for the formation of collagen and intercellular matrix, and hence, for the development of cartilage, bone and teeth and for healing of wounds. It influences the formation of hemoglobin, erythrocyte maturation, certain immunological reactions of the body and the conversion of folic acid to tetrahydrofolate.

Ascorbic acid is involved in carbohydrate metabolism and in the oxidation of phenylalanine and tyrosine. Scorbutic animals exhibit hyperglycemia, lowered glucose tolerance and resistance to insulin.

Large amounts of ascorbic acid are present both in the adrenal cortex and in the medulla. Its exact role at these sites, however, is not understood.

Ascorbic acid deficiency leads to the development of scurvy. The characteristic features in adults are perifollicular hemorrhages, petechiae, ecchymoses, particularly in "saddle areas" and posterior thighs, hemorrhages in subcutaneous tissues, muscles or joints; swollen, inflamed, bleeding and spongy gums and a normocytic or a microcytic anemia. In infants, loss of appetite, listlessness and subperiosteal hemorrhages leading to tenderness and restriction of limb movements are the cardinal features. Ecchymoses and gum changes similar to adult scurvy may also be seen. Infantile scurvy is usually seen in bottle-fed babies as human milk contains appreciable amounts of ascorbic acid.

Patients suffering from extensive and deep burns, those placed on a restricted diet for peptic ulcer and patients suffering from malabsorption syndromes may also develop ascorbic acid deficiency.

Absorption, fate and excretion: Ascorbic acid is synthesized in the liver by majority of the animals except man and guinea pigs and hence, deficiency of ascorbic acid can be produced in these two animal species only.

The minimum daily requirement of ascorbic acid for an adult is about 30 mg. and for infants, 5 mg. per kg. of body weight.

Ascorbic acid is readily absorbed from the gastrointestinal tract. After absorption, it circulates in the plasma and is concentrated in glandular tissue. The leucocyte and the platelet levels of ascorbic acid are higher than the corresponding plasma levels.

Ascorbic acid is partly metabolised and excreted in urine as oxalate and a part is eliminated in the free form. Urinary excretion depends upon saturation of body stores and in individuals with ascorbic acid deficiency, the vitamin may not appear in urine even on administration of large doses orally or parenterally.

Ascorbic acid is essentially non-toxic.

Preparations and dosage:

(i) Ascorbic acid tablet I.P. contains 50 mg. of the vitamin. Dose: Prophylactic, 25 to 75 mg. daily; therapeutic, 200 to 500 mg. daily.

(ii) Ascorbic acid injection I.P. contains 500 mg. of ascorbic acid in 2 ml. Dose: 0.1-1 g. I.M. or I.V.

Therapeutic uses: In the treatment of scurvy, ascorbic acid is administered in the dose of 100 to 500 mg. per day. As a prophylactic measure, it is important to ensure adequate Vitamin C intake in infancy and old age. Infantile scurvy can be prevented by adding 5 mg. of the vitamin to the feeds of bottle-fed infants. For prophylactic purposes, a daily dose of 50-100 mg. is advocated. Ascorbic acid increases the absorption of iron from the gastrointestinal tract by facilitating the conversion of ferric into ferrous form.

Because of its ability to function as a reducing agent, ascorbic acid in the daily dose of 300 to 600 mg is used in the treatment of methemoglobinemia; it is, however, less effective than methylene blue. The vitamin is also used as an antioxidant in emulsions of fats and oils, in certain injections and eye drops, and as a preservative.

Although it is claimed that daily prophylactic administration of Vitamin C (200-2000 mg) exerts a significant effect against the common cold, the evidence at present is controversial. Levels of ascorbic acid are known to fall during cold and other infections. This is probably a non-specific phenomenon and no connection has been convincingly demonstrated between Vitamin C and common cold which is a virus illness. Prescription of Vitamin C in the dose of 50 mg daily may, however, be valuable in those individuals who have an inadequate dietary intake of Vitamin C. Lastly, it must be pointed out that ingestion of large doses of Vitamin C can result in increased urinary excretion of oxalate and possibly kidney damage.

Ascorbic acid has been used empirically in a wide variety of conditions including nonspecific hemorrhagic states, anemia and dental infections without any benefit.

Table 69.1: Recommended Dietary Allowances of Various Vitamins for Adults per Day

Vitamins	Recommended by *ICMR for Indians	 WHO/FAO Expert Group
Thiamine	1.2-2.0 mg	1.0-1.5 mg
Riboflavin	1.3-2.2 mg	1.3-2.1 mg
Pyridoxine	—	1.5-2.0 mg
Niacin	16-26 mg	—
Vitamin B_{12}	1 μg	2 μg
Folate	100 μg	200 μg
Vitamin C	50 mg	30 mg
Vitamin A	750 μg	750 μg
Vitamin D	5 μg (200 I.U.)	2.5 μg (100 I.U.)

*ICMR—Indian Council of Medical Research.

Multivitamin combinations: Prophylactic multivitamin preparations should contain from one-half to one and one-half times the recommended dietary allowances except for vitamin D which should not exceed the daily recommended dietary allowance. Larger doses of ascorbic acid and B-complex in such preparations are wasteful, though not harmful.

Routine prophylactic supplementation of vitamin D should be avoided in normal subjects especially in infants and children who are taking adequate diet. Pyridoxine supplements interfere with the effectiveness of levo-dopa in the treatment of parkinsonism.

Multivitamin preparations for therapeutic uses may contain 4-5 times the recommended dietary allowances. Selective deficiency of a single vitamin B factor occurs less commonly and hence, combined B-complex therapy is commonly employed prophylactically as well as therapeutically in the management of generalised avitaminosis. Multivitamin therapeutic preparations should be used only for deficiency states and during increased vitamin requirements. Used indiscriminately as dietary supplement to 'keep up the energy and strength', they act no better than placebos and are wasteful and even harmful. Further, some of these preparations are quite expensive as they contain massive doses of water soluble vitamins most of which are washed out in the urine within 24 hours.

70 Vaccines and Sera; Immuno-suppressants and Immuno-stimulants

The science of immunology, though a very old one, has progressed rapidly in recent years. Today, it embraces not only preventive inoculation but has extended its boundaries to autoimmune diseases, allergic reactions and rejection mechanisms during organ or tissue transplants.

The mechanism by which body produces antibodies to an antigen is still obscure. However, it is interesting to note that this antibody formation system learns at an early stage during the foetal development to recognise 'self', as opposed to 'foreign' antigens against which specific antibodies are produced.

Immunological agents, which produce active or passive immunity, are used to prevent or to modify certain infectious diseases. That some of these agents have been spectacularly successful is attested by the remarkable decline of diseases such as small-pox, cholera, and poliomyelitis. Despite this success, the need for maintaining adequate antibody levels among the population is testified by the occasional outbreaks of cholera and small-pox which occur in certain countries.

Immunity can be defined as the ability of the body to neutralise and eliminate the pathogenic micro-organisms and their toxic products. It is subdivided into: (a) active immunity and (b) passive immunity.

(a) **Active immunity:** This type of immunity is due to the development of antibodies by the individual himself. Such an active immunity can be natural and species specific e.g. the relative immunity of horses, dogs and rats to tuberculosis, or can be acquired by introduction of the antigen.

(b) **Passive immunity:** When immunity is acquired passively by the transfer of antibodies from the donor serum to the recipient, it is called as passive immunity. Passive immunity can be acquired naturally e.g. in foetus receiving maternal antibodies across the placenta, or artificially by the administration of antisera containing the antibodies.

The various preparations employed for conferring immunity are:

1. **Vaccines:** Vaccines are suspensions of dead or attenuated microorganisms which stimulate the reticuloendothelial system of the host resulting in the development of one or more type of antibodies. Vaccines are employed prophylactically and are of no value if administered during the incubation period or in the active stage of a disease. A vaccine, however, may be used as general stimulant of the reticuloendothelial system in conditions like gonorrhoeal arthritis and undulent fever and for production of specific antisera against *streptococci, pneumococci* etc. in animals. In general, vaccines containing live, attenuated microorganisms are antigenically more potent than those made up of killed microorganisms.

II. **Toxoids:** Toxoids are produced by addition of formalin to the toxins of microorganisms and incubating them at 37°C for 3 to 4 weeks. This results in loss of toxicity without reducing the antigenicity. Toxoids provoke antibody response both in humans and in animals.

III. **Immune animal serum (antiserum):** This is the serum obtained from animals like horse and rabbit which are previously injected with a vaccine, a toxin or a toxoid. The sera of such animals contain antibodies either against the microorganisms or their toxins.

Antisera containing antibodies against the toxins of *C. diphtheriae, Cl. tetani* and *Cl.*

welchi are widely used.

IV. **Immune human sera:** These are derived from convalescent, immune or hyperimmunized adults. Thus, human hyperimmune antitetanus serum is now employed in preference to ATS of animal origin.

V. **Immunoglobulin** (Human): Formerly termed as gamma globulin, this agent is a refined product prepared from pooled human blood plasma having a high antibody titre. Placentae of mothers immunized with the administration of a toxoid a few weeks before delivery have also been used as a source.

Active immunization with vaccines and toxoids may be primary or secondary.

Primary immunization is commonly carried out in infants and in children to induce primary immunity and consists of administering two or more doses of the vaccine or toxoid at suitable intervals. A mixture of 2 or more vaccines e.g. T.A.B. with cholera or vaccine-toxoid mixtures such as diphtheria and tetanus toxoid with whooping cough vaccine, may be employed for primary immunization and is termed combined immunization.

Secondary immunization is carried out to reinforce the primary immunity by giving a single 'booster' or 'recall' dose of the antigen. It may be carried out during an epidemic, before undertaking a journey to endemic zones, or as a routine procedure in a planned immunization programme in children.

The common vaccines and toxoids employed for active immunization are summarized in Table 70.1.

Table 70.1: **Vaccines and Toxoids**

Source	Widely accepted	Moderately accepted
Bacterial vaccines	Whooping cough, Typhoid, Cholera, Plague	Tuberculosis
Rickettsial vaccines	—	Epidemic typhus
Viral vaccines	Smallpox, Yellow fever, Measles, Poliomyelitis, Rabies	Mumps, Influenza, Rubella
Bacterial toxoids	Diphtheria Tetanus	—

BACTERIAL VACCINES

The important bacterial vaccines used in practice are given in Table 70.2.

Table 70.2: **Bacterial Vaccines in Common Use**

Vaccine	To be given at age	First dose ml.	Addl. doses and interval	Booster Dose
Pertussis	2-4 months, I.M.	0.25-0.5	Two doses monthly	2 years and again at 4-6 years
Typhoid-paratyphoid A, B (TAB, alcohol treated)	After 2 years at any age, I.M. or S.C.	0.25 (adult)	0.5 ml., 4 weeks	Every year, 0.3 ml. in endemic area
Cholera	After 1 year at any age, I.M. or S.C.	0.5 (adult)	1 ml., 2-4 weeks	Every year in endemic area
Cholera formalised	-do-	0.1-0.2 1-4 years 0.2-0.3 5-10 years	0.2-0.3 ml., 2-4 weeks	-do-
Plague	After 2 years at any age, I.M. or S.C.	0.5 (adult)	1 ml., 2-4 weeks	1 ml., every year in endemic area

All these vaccines contain killed micro-organisms.

Cholera and TAB vaccine can be administered together.

Adverse reactions to vaccines are generally mild and consist of local tenderness, erythema, induration, fever and malaise. Allergic reactions are not common but can occur particularly if the organisms are grown on foreign protein material such as egg protein from chick embryo tissue culture. Any vaccine produced from the organisms grown in chick embryo culture is contraindicated in patients allergic to eggs, chicken or chicken feathers. Generally, vaccines (particularly those containing live organisms) are contraindicated in the presence of an acute illness, in patients with debilitating diseases or agammaglobulinemia and in patients receiving corticosteroids, antineoplastic drugs, immunosuppressive agents or radiotherapy. Live virus vaccines are usually avoided during pregnancy for fear of infecting the fetus.

PERTUSSIS VACCINE I.P.: This is a sterile suspension of whooping cough bacilli, *Haemophilus pertussis.* Although it can be given alone, it is usually administered along with tetanus and diphtheria toxoids. This vaccine should be given early in life as three-fourth of the deaths due to whooping cough occur in infancy. It is usually not advisable to administer this vaccine to those over 6 years of age because whooping cough after this age is nearly always mild and the incidence of adverse reactions to this vaccine is higher. The complications are provocation of poliomyelitis and convulsions. Hence, the vaccine should not be used in the presence of infection, in children with a history of central nervous system disturbances and in those with an allergic diathesis.

TYPHOID-PARATYPHOID A AND B VACCINE (T.A.B. Vaccine) I.P.: This is a sterile suspension of *S. typhi* and *Paratyphi A* and *B* bacilli. As typhoid fever is very rare in children below 3 years, primary immunization below this age is unnecessary. Doses of alcohol-treated vaccine are 0.25 ml. initially, followed by 0.5 ml. after 1 to 4 weeks by subcutaneous or intramuscular route. The heat-killed bacilli vaccine is used in the dose of 0.5 ml. and 1 ml. respectively at 1-4 weeks interval. Immunity with this vaccine is not complete and it protects only 70-90% of the recipients against typhoid as that obtained following typhoid fever. Typhoid patients, treated with chloramphenicol at an early stage of the disease, fail to develop antibodies and should be subsequently immunized with three injections of the vaccine, 0.1 ml. intradermally.

The vaccine usually gives mild local and systemic reactions such as pain, bodyache, headache and fever. Intradermal inoculation has been demonstrated to have a lower incidence of adverse reactions. For this purpose, two doses of 0.1 ml. are given intradermally at the interval of 28 days. The same dose may be repeated as a booster. Alcohol or acetone preparations are unsuitable for intradermal use.

Paratyphoid vaccine (A and B) which is combined with typhoid vaccine has been shown to be ineffective. In fact the combined preparation gives rise to adverse reactions more frequently than typhoid vaccine alone and, therefore, should be avoided.

CHOLERA VACCINE I.P.: This is a suspension of heat killed, suitable strains of cholera vibrio. Immunity appears within 7 to 10 days and lasts for 3 to 6 months. Reactions are usually mild and can be minimised by using intradermal route, the dose being 0.1 ml.

CHOLERA VACCINE FORMALISED I.P.: This is an uncontaminated culture of vibrios, killed by the addition of formaldehyde. It is administered according to the same dosage schedule as cholera vaccine, but a single dose of 1 ml. may be given subcutaneously in an emergency.

In general, the cholera vaccines available at present provide only about 50% effectiveness for about 3-6 months even with 2 doses and do not prevent the transmission of cholera. Further, the conventional vaccine may not modify the severity of symptoms in vaccinated cholera patients. Hence, various new vaccines are under investigations.

PLAGUE VACCINE: This is a sterile suspension of suitable strains of *Pasteurella pestis.* As the immunity with this agent is of short duration, persons exposed to infection should be given a booster dose of 1 ml. every year. In an emergency, a single dose of 3 ml. may be administered. This vaccine gives more severe febrile reaction than T.A.B. vaccine and regional lymph nodes may get enlarged.

FORMALISED PLAGUE VACCINE I.P. is prepared by killing an uncontaminated *P. pestis* culture by the addition of formaldehyde. Dose: 1 ml. subcutaneously followed by 1 ml. after 7-10 days. In an emergency, single dose of 3 ml. may be given.

B.C.G. VACCINE: Discussed in Chapter 47.

RICKETTSIAL VACCINE

TYPHUS VACCINE I.P.: Typhus vaccine is a sterile suspension of epidemic and murine typhus rickettsiae grown in chick embryo culture. Dose: 0.25 to 1 ml. subcutaneously at interval of 7 to 10 days. A reinforcing dose of 1 ml. should be given annually, except during an epidemic when it should be administered at the interval of 3 months. The vaccine may occasionally induce mild allergic reaction.

Apart from its use in epidemic and murine typhus, the vaccine is also useful in the prophylaxis against louse-borne and flea-borne typhus.

VIRAL VACCINES

SMALLPOX VACCINE (Vaccine Lymph) I.P.: It contains the living virus of vaccinia. The storage of lymph vaccine is of great importance. Kept below the freezing point, it retains potency for six months whereas when stored between 0° and 5°C the potency is retained only for a month. The immunity against smallpox conferred by this vaccine lasts for 5 to 7 years. However, in countries like India where the disease is endemic, revaccination is advised every 4th year and in the event of special risk. The international vaccination certificate for smallpox is valid only for 3 years.

Freeze-dried vaccine has now replaced the time honoured glycerinated lymph vaccine because of obvious advantages. It is very stable for many months even at temperatures 37-40°C, has greater purity and is free from contaminating bacteria and tissue debris.

Smallpox vaccine, 0.06 ml., is inoculated intradermally by scarification or multiple pressure. The successful primary vaccination is characterised by the development of a pustule leading to formation of an ulcer which heals by scarring. The reaction is associated with generalised symptoms like fever.

Precautions, contraindications and adverse reactions: Generally, all other preventive inoculations should be avoided within 3 weeks of primary smallpox vaccination. The routine vaccination of pregnant women should also be avoided for the danger of causing encephalitis in the foetus. Pregnancy, however, is not a contraindication to vaccination if there is a serious risk of exposure of smallpox infection.

The contraindications to vaccination are the presence of septic skin infections, hypogammaglobulinemia, acute febrile illness, allergic eczema and leukemia. It is necessary to enquire about the incidence of eczema in family members. It is also contraindicated in patients with history of convulsions and in those receiving irradiation or therapy with corticosteroids, alkylating agents and antimetabolites.

A common and serious complication is eczema vaccinatum, occurring in subjects with eczema. Even contact with a vaccinated person may cause this complication in a susceptible child due to accidental transfer of the virus. It is treated by giving hyperimmune antivariola gammaglobulin

0.44 ml. per kg. Postvaccinal encephalitis though rare is a dangerous complication with a high mortality rate.

For conferring immediate protection from smallpox during an epidemic, methisazone may be useful. This is discussed in Chapter 53.

YELLOW FEVER VACCINE I.P.: This consists of a suspension of chick embryo tissue infected with yellow fever virus. The dried product is reconstituted with saline or some other appropriate diluent before use. The dose is 0.5 ml. of the reconstituted vaccine. It may be repeated every 6 years.

Immunity after vaccination is usually established within 10 days and persists for 6 years. The vaccine may occasionally cause serious encephalitis.

MEASLES VACCINE: At present, two types of measles vaccines are available in Western countries. These are: (a) the inactivated measles vaccine and (b) the attenuated, live measles vaccine, containing the attenuated live measles virus.

Most of the strains used for measles vaccine are developed from the original Edmonston 'B' strain of attenuated measles virus deriving its name from the patient David Edmonston, from whom the virus was isolated.

(i) *Inactivated measles vaccine*: This is a sterile suspension of the Edmonston strain of virus, inactivated by formaldehyde. The vaccine induces active immunity in about 80 to 95 per cent of susceptible children and confers protection for at least 6 months when it is administered monthly for 3 months. The antibody titres achieved, however, are lower than those obtained after any of the attenuated live measles vaccines. If the inactivated vaccine is followed 4 to 6 weeks later by the live attenuated vaccine, immunity lasts longer and the incidence of untoward reaction to the live vaccine is also reduced.

Inactivated measles vaccine should be administered I.M. in children without history of measles at as early as 3 to 4 months of age. The initial dose is 0.5 to 1 ml. and two more doses of 0.5 to 1 ml. are given at monthly intervals. Transient local reaction and a febrile response may occur; a maculopapular rash or urticaria occasionally develops within 24 hours of injection and may persist for a few days. Allergic reactions are rare.

(ii) *The attenuated live measles vaccines*: These vaccines contain attenuated live Edmonston B strain of measles virus, grown in chick embryo or canine kidney tissue culture. A vaccine containing a further attenuated strain of the Edmonston virus has recently been made available (Measles vaccine attenuated, Schwarz). The vaccines are administered subcutaneously in the dose of 0.5 ml.

Both these vaccines induce active immunity in approximately 99 per cent of the recipients with a single dose. They produce a noncommunicable mild measles infection. A mild febrile response accompanied by a rash and occasionally by cough and coryza is often seen. The antibodies produced with live Edmonston B strain appear within 12 days and persist for as long as 8 years after vaccination.

The adverse effects following Edmonston B vaccination can be reduced by giving concomitantly, gamma globulin intramuscularly in doses of 0.009 to 0.04 ml./kg. This does not interfere with the antibody response. In comparison to Edmonston B vaccine, the incidence and severity of adverse effects with Schwarz live attenuated vaccine are much less while the immunity conferred is fairly comparable. Hence, the present trend is to give a single injection of attenuated, live measles vaccine (Schwarz vaccine).

Live measles vaccination carries the same precautions and contraindications as smallpox vaccination. In addition, it should be avoided during the first trimester of pregnancy, in children with active, untreated tuberculosis and in those allergic to egg protein. The measles vaccines do not confer immunity against rubella.

POLIOMYELITIS VACCINES: These vaccines are of two types: (1) the inactivated poliomyelitis vaccine and (ii) live oral vaccine.

(i) *The inactivated poliomyelitis vaccine* (Salk vaccine): This is an aqueous suspension of approved strains of poliomyelitis virus, types 1, 2 and 3, grown in culture of monkey kidney tissues and inactivated by a suitable method.

The Salk vaccine produces active immunity against paralytic poliomyelitis by producing serum antibodies specific for types 1, 2 and 3 poliovirus. It induces only limited resistance to growth of the virus in the intestine and thus, does not affect the carrier state (excretion of the virus in feces), which is an important factor in the spread of the disease. However, it is probably somewhat more reliable in stimulating a serum antibody titre.

The vaccine is given by subcutaneous or intramuscular injection, 3 doses each of 1 ml., at an interval of 4 to 6 weeks between the 1st and the 2nd dose, and 12 months between the 2nd and the 3rd. Adverse effects are usually mild and consist of local pain, erythema, induration and fever. Allergic reactions may occur very rarely.

(ii) *Live oral poliomyelitis vaccine N.F.* (Sabin vaccine): This is the most favoured antipolio vaccine at present and is available either in monovalent or in trivalent form. The former is an aqueous suspension of either types 1, 2 or 3 Sabin strain of attenuated poliomyelitis virus, while the latter contains all the three attenuated strains.

With oral vaccine, type specific immunity develops in 80 per cent or more of the recipients; specific serum antibodies appear within 7 days and the titre reaches a peak within 21 days. The exact degree and duration of immunity against paralytic poliomyelitis is uncertain but appears to be reliable and prolonged.

In addition to systemic immunity, the living poliovirus provides a localized resistance (intestinal immunity) to reinfection by the poliovirus. This leads to stoppage of fecal excretion of the virus and consequent elimination of the carrier state. Other enteroviruses, which are more prevalent in the summer months, may interfere with the intestinal implantation of live poliovirus vaccine strain.

Ideally, the oral polio vaccine should be administered in the monovalent form, types 1, 3 and 2 (or types 2, 1 and 3) given separately in 3 doses usually at monthly intervals. Each dose contains 200,000 to 500,000 tissue culture infective doses in 2 or 3 drops or in 2 ml., depending on the preparation used. The vaccination can be combined with the administration of triple antigen (whooping cough, diphtheria, tetanus). After primary immunization, reinforcement should be carried out 1 year after the 3rd dose, at 6 and again around 10 years of age.

The trivalent poliovirus vaccine is given in 3 doses at the interval of 4 to 8 weeks; a booster dose is indicated 12 to 15 months after the third dose and another at the time of school entry. The trivalent oral vaccine may also be used to reinforce the immunity induced with Salk vaccine.

No serious adverse effects have been reported so far with these vaccines. Epidemiological data suggest that there may be an extremely small risk of paralytic disease following the oral vaccine, especially type 3, although a definite cause-effect relationship cannot be established.

The only contraindications to the use of oral polio vaccine are the presence of acute infection and diarrhoea. History of tonsillectomy or of adenoidectomy is no contraindication to its use. There are no data available which would contraindicate the use of this vaccine during pregnancy.

In India, most of the children above the age of 7 years have adequate polio antibody titres in their sera and vaccination in children above 8 years is probably unnecessary.

CARBOLISED RABIES VACCINE I.P.: This is a sterile suspension of brain substance containing fixed virus of rabies, inactivated by the addition of phenol. Commonly, the brains of sheep inoculated subdurally with the brain substance of a rabies-infected rabbit are used for preparation of the vaccine.

The vaccine is used for prevention of rabies in patients who have been bitten by suspected rabid animals; in a doubtful case, the treatment is stopped if the animal remains normal on 10th day after the bite.

After thorough cleansing and local treatment for the bite, the case is graded by considering (i) the number, depth, severity and position of bites, (ii) whether the bite was inflicted through clothing, (iii) any treatment given previously and (iv) the time elapsed since bite (if 4 or 5 days have elapsed more prolonged treatment is required). Licks or slight cuts and abrasions may be treated less vigorously, as rare but serious neuroparalytic complications can follow rabies vaccination.

The vaccine is given subcutaneously into the cellular tissue on the side of the abdominal wall below the costal margin. The inoculation site should be changed with every dose and the patient should be asked to avoid fatigue-provoking activities. Immunity conferred by the vaccine lasts for approximately 3 months. It is, however, incomplete and unpredictable.

For light treatment, a total dose of 40 to 50 ml. is given in divided doses over a period of 2 weeks; for medium treatment, a total of 60 to 65 ml. should be given over 3 weeks and for intensive treatment, a total of 80 to 85 ml. is given over the same period. During intensive treatment, the antiserum should be infiltrated around the wound locally and injected intramuscularly within 24 to 48 hours of the bite followed by vaccine therapy.

The dose of the vaccine for a child less than 12 years of age is half or three quarters that of the adult. The maximum single dose of the vaccine is 4 ml. for an adult and 2 ml. for a child.

Apart from local induration, erythema and regional lymphadenopathy, neurological complications such as polyneuritis, myelitis and encephalomyelitis have been occasionally described following rabies vaccination. A vaccine obtained from duck embryo tissues infected with fixed rabies virus is available. This is preferred to the nervous tissue vaccine because of the lower possibility of neuroparalytic complications. It is administered in the same manner but in addition, two supplemental doses are given 14 and 20 days after cessation of therapy, particularly in serious cases.

Recently, human diploid cell vaccine prepared in human fibroblasts has been developed and is under investigation. It is claimed to give antibody response equal to that of 14 injections of conventional vaccine with only a four dose schedule.

MUMPS VACCINE: Reduction in the incidence of mumps has been shown among persons vaccinated with either inactivated virus preparation or with a live attenuated virus. The latter is preferred. It is a suspension of Jeryl Lynn strain grown in chick embryo tissue culture. Following a single injection, it produces active immunity in 95% of subjects. Adverse reactions are uncommon and mild.

INFLUENZA VACCINE: Highly purified adsorbed bivalent influenza vaccine is now available. It contains antigen from inactivated influenza virus A and virus B (Hongkong strain). It produces immunity within 2-3 weeks. A single dose may give protection for 6 months. Adverse reactions are infrequent and include allergy and polyneuritis. A drawback of all influenza vaccines is the frequent changes in the infective strains of the virus with changes in their antigenic properties. Hence, the efficacy of these vaccines is variable. The vaccine may be particularly useful in old and chronically ill patients.

RUBELLA VACCINE: This vaccine, containing the attenuated RA 27/3 strain of rubella virus, has been administered prophylactically subcutaneously. Antibodies following vaccination develop within 6 weeks of inoculation. The same vaccine, administered intranasally in the form of drops has been demonstrated to produce a comparable immunity. The latter procedure will undoubtedly be of great value in mass prophylaxis against rubella.

BACTERIAL TOXOIDS

DIPHTHERIA TOXOID: This is a detoxified preparation of toxin produced by *Corynebacterium diphtheriae*. It includes the formol toxoid (F.T.), the toxoid antitoxin floccules (T.A.F.) and natural adjuvant factor toxoid (N.A.F.T.). In addition, preparations are available in which the diphtheria toxoid is adsorbed on a suitable mineral carrier. These include the alum precipitated toxoid (A.P.T.), purified toxoid aluminium hydroxide (P.T.A.H.) and purified toxoid-aluminium phosphate precipitated (P.T.A.P.).

Purified forms are now preferred because of the lower incidence of adverse reactions. The diphtheria toxoid-mineral complexes release the toxoid gradually and thus provide a prolonged antigenic stimulus. The alum precipitated toxoid (A.P.T.) is usually preferred in children under 5 years of age as it rarely causes allergic reactions in this age group. It may, however, cause serious reactions in older children and in adults, for whom PTAH or PTAP is recommended. These, in addition, can also be used in children below 5 years of age. Incidence of associated poliomyelitis is higher with APT, PTAH and PTAP, in comparison to FT and TAF. However, this danger is now greatly reduced following widespread immunization against poliomyelitis. Toxoid antitoxin floccules (TAF) is suitable in older children and adults who are likely to develop some form of reaction to the other preparations. However, it contains horse serum proteins and is unsuitable in sensitized subjects.

Primary immunization for diphtheria is carried out in the first year of life, preferably from 4 to 6 months. Various preparations are given intramuscularly or subcutaneously. The preparation commonly used for this purpose is diphtheria, tetanus and whooping cough vaccine. This is discussed later. Immunization for diphtheria alone may be carried out as follows:

For children under 5 years: PTAP or PTAH dose 0.5 ml., two doses at the interval of 4 to 8 weeks. A third dose of 0.5 ml. may be given 6 months after the second dose and a booster given at school entry.

For children between 5 and 10 years: PTAP or PTAH, dose 0.2 ml. In the absence of a reaction, a second dose of 0.5 ml. should be given 4 weeks later.

For children over 10, adolescents and adults: All individuals over 10 years should be tested for sensitivity reaction by giving 0.1 ml. of 1 : 10 dilution of fluid toxoid (Moloney test). The development of local reaction (severe pseudo-Schick reaction) is a warning that toxoid must be administered cautiously in multiple, small, suitably diluted doses; TAF is often suitable in such cases. In those not showing the reaction, TAF may be administered in two doses of 0.5 ml. at the interval of 4 weeks.

In the event of an epidemic, the Schick test must be carried out in all children and adolescents, not immunized previously. The Schick positive individuals should then be immunized suitably according to the age group as mentioned earlier. However, they should also be given 500 to 2000 units of purified antitoxin for immediate protection, which lasts for about 2 weeks.

The adverse effects reported include pyrexia, local reactions, formation of nodules and cysts, especially with aluminium containing preparations. They may also provoke poliomyelitis infection and allergic reactions. Encephalitis and convulsions may occur rarely.

DIPHTHERIA, TETANUS AND WHOOPING COUGH VACCINE: This is a mixture of diphtheria formol toxoid, tetanus toxoid in simple solution and whooping cough vaccine. It has the advantage of reducing the number of primary injections and, possibly, of increasing the antigenicity of diphtheria and tetanus vaccines. Usually, a dose of oral poliomyelitis vaccine is advocated along with every dose of triple antigen. The triple antigen is given in 3 doses of 0.05 ml. at 4 to 6 weeks interval, with an additional reinforcing dose of 0.5 ml. given in the 3rd or the 4th year.

If, for any reason, the second injection has not followed the first within 4 to 6 weeks, the first dose should be ignored and the course started again.

The combined vaccine should not be given in children with history of fits, convulsions, eczema, asthma or an allergic disease in the child or near relatives, and during an acute illness or recovery from such an illness.

TETANUS TOXOID I.P.: Tetanus toxoid is prepared from tetanus toxin produced by *Clostridium tetani*. It is available in the following forms:

(i) tetanus toxoid in simple solution, (ii) alum precipitated tetanus toxoid, (iii) purified toxoid aluminium hydroxide, and (iv) purified toxoid aluminium phosphate (PTAP).

The immunity produced by tetanus toxoid is greater and of longer duration than that obtained with tetanus antitoxin. For primary immunization, the toxoid is administered either alone, or usually with whooping cough and diphtheria antigens, preferably within the first year but after 3 months of age. When used alone, the tetanus toxoid in simple solution is administered either subcutaneously or intramuscularly in 3 doses of 0.5 ml. The interval between the 1st and the 2nd dose should be 6 to 12 weeks and the 3rd dose should be given 6 to 12 months after the second dose. A reinforcement dose of 0.5 ml. may be given 5 years after the third dose. Neonatal tetanus can be prevented by giving the mother two doses of 0.5 ml. of the adsorbed toxoid 6 weeks apart, in the second trimester of pregnancy. Aluminium containing preparations have the same dosage schedule.

PTAP which has a slower but sustained action is now considered superior to fluid toxoid for primary immunization but the latter is preferred for booster doses as its action is more rapid in onset. In addition, PTAP is effective when given concurrently with ATS whereas the action of fluid toxoid is antagonized by ATS.

Allergic reactions to tetanus toxoid are rare but have been reported. The aluminium containing preparations may rarely provoke poliomyelitis and allergic reactions.

Active immunization programme: Majority of the serious infections with a high mortality and morbidity rate can now be successfully prevented by prophylactic immunization. Such immunization must now form an important aspect of child welfare programme in the community. Combined prophylaxis reduces the number of visits, the incidence of untoward reactions and the cost.

It is generally believed that the neonate is immune to a majority of infections because of maternal antibodies; such immunity, however, may last for only first 6 to 10 months. It has been demonstrated that the newborn does not have any immunity against tuberculosis. Immunoprophylaxis, therefore, is recommended right from birth so as to build up a substantial active immunity against a number of viral and bacterial infections, within first few months of life. Subsequently, the antibody titre can be maintained or augmented by administration of 'booster doses' of antigens at regular intervals.

An immunization schedule suitable for children in India is given in Table 70.3.

The schedule may be modified in developed countries. Thus, the administration of BCG may be postponed to a late period and smallpox and TAB vaccines may be given only in the event of a special risk.

PASSIVE IMMUNIZATION

Passive immunization consists of administration of antibodies in the form of serum, plasma or immunoglobulin to a person who

Table 70.3: **Suggested Immunization Schedule in India**

Vaccine	Primary immunization	Reimmunization
B.C.G.	Birth, single dose	7 and 14 years
Small pox	1st to 3rd month—single dose	Every 4th year and in event of special risk
Triple (Diphtheria, tetanus, whooping cough) with oral poliomyelitis	2nd to 4th month (monthly x 3 doses)	12 months to 2 years, and once again at 5-8 years
Measles Schwarz	10th month, single dose	—
*Typhoid, paratyphoid	2nd to 4th year	Every year
Diphtheria Tetanus (adsorbed)	6 to 10 years	8th and 12th year

*This can be given along with cholera vaccine.

is exposed to infection but in whom the disease has not actively developed. The major advantage of passive immunization is availability of readymade antibodies against the imminent infection; such immunity, however, lasts only for a short period. In addition, passive immunization is often associated with unpleasant allergic reactions including fatal anaphylaxis, particularly when a heterologous serum is used. Some authorities use adrenaline, glucocorticoids and an antihistaminic prophylactically with the hope of preventing such serious reactions. The recent trend, however, is to use homologous antibody preparations and concentrated immunoglobulins.

It is advisable to determine the sensitivity of the patient before giving him an injection of an antiserum regardless of whether or not he has previously received an injection of animal serum.

The skin test dose is 0.02 ml. of a 1 : 100 dilution of the serum injected intradermally. In subjects with a history of allergy it should be reduced to 0.02 ml. of a 1 : 1,000 dilution. The test is considered as positive if a wheal develops within 30 minutes. For the eye test, one drop of a 1 : 1,000 dilution of serum in normal saline solution is put into one eye; one drop of normal saline alone is instilled into the other eye as a control. The patient is considered as allergic if the treated eye shows lacrimation and conjunctivitis within 30 minutes. The skin test is generally preferred because it is less risky.

A patient who is allergic but needs the antiserum can be desensitized by injecting small, graded doses of the antiserum. Thus, the following doses are injected either subcutaneously (s.c.) or intramuscularly (i.m.), generally at 15 minutes intervals, the next dose being injected if there is no reaction to the previous one:

0.05 ml of 1 : 20 dilution, s.c.
0.1 ml of 1 : 10 dilution, s.c.
0.3 ml of 1 : 10 dilution, s.c.
0.1 ml of undiluted serum s.c.
0.2 ml of undiluted serum i.m.
0.5 ml of undiluted serum i.m.

Finally, the entire remaining dose is injected intramuscularly. In case of anaphylaxis 0.5 ml. of adrenaline 1 : 1,000 is injected intramuscularly (less dose in children) and repeated if necessary every 5-15 minutes. For details see Chapter 20.

The important preparations available for therapy are:

DIPHTHERIA ANTITOXIN I.P.: This

is a serum preparation from horse, actively immunized against *C. diphtheriae*. It contains the antitoxic globulins or their derivatives that have the specific power of neutralising the toxin of these organisms. It has a potency of not less than 1000 units per ml.

Diphtheria antitoxin neutralizes the diphtheria toxin locally at the site of infection and also that circulating in the blood. However, it is probably ineffective in neutralising the toxin fixed to the tissues, nor can it reverse the pathological changes already induced by the toxin.

The dose of the antitoxin varies not with the age of the patient but according to the severity and stage of the disease. As the mortality increases rapidly with the delay in administration of the antitoxin, an intramuscular injection of at least 4,000 units should be immediately given to all suspected cases even before taking throat swabs. The physician should then judge the severity of the case clinically and administer the additional dose without waiting for the results of investigations which may take several days.

The dosage range of antitoxin is still controversial, but in mild diphtheria confined only to the nasal or laryngeal regions, a dose of 8,000 units by intramuscular injection is usually adequate. Moderately severe cases require 10,000 to 30,000 units intramuscularly. Larger doses may be used in more severe cases. In all severe cases, a portion of the dose is given intramuscularly, followed 1½ to 2 hours later by the bulk of the dose intravenously. The intramuscular injection should be given in the lateral aspect of the thigh after ascertaining the absence of hypersensitivity to the serum. In no case should the intravenous administration precede the intramuscular dose nor should it be resorted to in individuals with an allergic diathesis or a family history of allergic disorders.

Passive protection is also required for Schick positive individuals in close contact with diphtheria patients and has been discussed earlier. The immunity thus provided lasts only for 2 weeks and hence, such cases should also be immunized actively at the same time.

The adverse reactions to the anti-serum include localised or generalised hypersensitivity reactions, vasovagal attacks, pyrexia and anaphylactic shock.

Hypersensitivity reactions can be minimised by noting the patient's reactivity before intramuscular administration of the serum.

Vasovagal reaction which occasionally develops should be treated by giving a head-low position and by the use of sympathomimetic vasopressor agents. Febrile episodes can be minimised by strict asepsis, use of purified serum and by giving it slowly. Pyrexia can be controlled by salicylates and tepid sponging.

The use of penicillin and erythromycin in diphtheria is discussed in Chapter 41.

TETANUS ANTITOXIN I.P.: This is a serum preparation from the horse, actively immunized against the toxins of *Cl. tetani*. It contains the antitoxic globulins that can neutralise the tetanus toxin.

The prophylactic dose of the antitoxin is 1,500 to 3,000 units, administered by subcutaneous or intramuscular injection, after preliminary testing. The immunity conferred wears off within 1 to 3 weeks. At present, there are two views regarding tetanus prophylaxis. One group believes that use of ATS is of negligible value and moreover is likely to cause serious serum reactions. Hence, they recommend wound toilet, antibiotic therapy with penicillin or a tetracycline and active immunization by means of tetanus toxoid. ATS is given only in heavily contaminated wounds of more than 12 hours duration. The available evidence, however, does not clearly prove that ATS is totally useless nor does it show that only antibiotics and wound toilet give complete protection. There is no doubt that adequate wound excision and toilet are essential but are sometimes impracticable particularly in a country like India, with such a high incidence of tetanus. Hence, in areas where tetanus is almost endemic, severely contaminated or deep penetrating wounds should be treated with wound toilet, ATS and a course of antibiotic to give the maximum protection. Clean wounds or small abrasions or lacerations should be treated without ATS. It must be noted that a second dose of ATS, in a patient who has received ATS once before, is very rapidly eliminated and hence, is ineffective. In such cases, active immunization should be started at once.

Of course, the ideal thing to do is to immunize everyone in the country by tetanus toxoid injections.

TETANUS IMMUNE GLOBULIN (Human): This is a sterile solution containing 165 ± 15 mg. of gamma globulin per ml. prepared from human plasma having a high titre of tetanus antitoxin. Such plasma is obtained from blood of hyperimmunized subjects, or from placentas from mothers who have received tetanus booster inoculations a few weeks before delivery. Because of its human origin, the preparation is less prone to cause serious allergic reactions.

The half life of human immune globulin is between 3 to 4 weeks. Its prophylactic dose is 250-500 i.u. intramuscularly. Active immunization with tetanus toxoid should be carried out simultaneously.

No serious adverse effects with this agent have been reported so far.

GAS GANGRENE ANTITOXIN: Monovalent antitoxins neutralising the toxins of *Cl. oedematiens, Cl. septicum* and *Cl. welchii* are available. These are not much useful in practice because of the difficulty in rapidly identifying the infecting organism.

The mixed gas gangrene antitoxin I.P. contains not less than 1,000 units each of Oedematiens and Welchii antitoxin and not less than 500 units of Septicum antitoxin. It is given as a prophylactic measure as soon as possible after the injury, in the dose of 25,000 units I.V. or I.M. The dose may be doubled or repeated if the clinical condition deteriorates or if operative interference is required.

The therapeutic dose is 75,000 units, preferably intravenously. The efficacy of local injection in the region around the wound is doubtful. Tetanus and gas gangrene antitoxins may be administered simultaneously if necessary.

BOTULINUM ANTITOXIN: This is a horse serum preparation, containing the antitoxic globulins which neutralise the toxins formed by *Cl. botulinum*, types A and B.

For effective treatment, the polyvalent antitoxin must be administered in the very early stage of botulism. For this purpose, not less than 50,000 units should be injected every 6 to 12 hours intravenously; the antitoxin may also be given prophylactically in individuals who have ingested the suspected food but have not yet developed the symptoms, in the dose of 10,000 units of each type by intramuscular injection.

RABIES ANTISERUM: This is an animal serum containing the globulins that have the specific power of neutralising the rabies virus. It contains not less than 80 units of activity per ml. of serum. It is usually given along with rabies vaccine in patients who have received severe bites. For this purpose, not less than 400 units are infiltrated round the wound and at the same time, a dose of 40 units per kg. is given intramuscularly. This is followed by administration of rabies vaccine. Its usefulness, however, is doubtful. The use of human immunoglobulin against rabies is still in an experimental stage.

IMMUNOGLOBULINS: These have been used for passive protection and are discussed in Chapter 53.

ANTI-D (Rho) IMMUNOGLOBULIN (Human): This is prepared from pooled plasma of naturally immunized women with high titre of anti-D antibodies or from the serum of suitably immunized males. When administered to Rh negative pregnant women with Rh positive husbands and Rh positive foetuses, in the dose of 250 microgrammes intramuscularly within 72 hours of delivery, it prevents rhesus immunization in the mother. It may thus prove valuable in the prevention of erythroblastosis foetalis in subsequent pregnancy. It acts by neutralising the foetal antigen which escapes across the placenta into the maternal circulation. Such escape usually takes place during delivery. Rho (D) immunoglobulin is contraindicated in Rh positive women and in Rh negative women who develop Rh antibodies because of a previous conception or transfusion of Rh positive blood. The preparation is to be given to the post partum mother and not to the neonate. It is also used after abortion, whether spontaneous or induced. Adverse reactions are usually mild.

ANTI-SNAKE VENOM SERUM: The poisonous snakes belong to three families—the Viperidae (phoorsa, rattle snake, daboia), the Elapidae (cobra, krait, mamba) and the Hydrophiidae (sea-snakes). The viper venom commonly kills by its action on the cardiovascular system, though some contain a neurotoxin as well. The elapid venom contains mainly a neurotoxin which causes muscle paralysis by its neuromuscular blocking action. Such paralysis is not always reversible with the antivenom, particularly in case of krait bite. However, it is naturally reversible after about two days and in such cases artificial respiration and intragastric feeding (because of glossopharyngeal palsy), in addition to antivenom therapy, could be life saving.

The dangers of poisonous snakebite in human victims appear to be greatly exaggerated. Nearly half of the people bitten by poisonous snakes such as cobra and vipers develop no significant systemic poisoning because of very low dose of the venom injected. Obviously, such patients need no antivenom therapy. Hence, in doubtful cases it is better to wait and watch the patient carefully for clear clinical evidence of systemic poisoning such as ptosis, limb and neck muscle paresis, blood stained sputum and failure of the blood to clot, before giving antivenom. However, such patients must be hospitalised and examined at half hourly intervals. Since antivenom can sometimes cause severe allergic reactions including anaphylaxis, sensitivity tests must be performed prior to its administration.

The Haffkine Institute, lyophilised, polyvalent, anti-snake venom serum (antivenin), obtained from immunized horses, contains the purified antitoxic globulins that have the power of neutralising the venom of cobra, krait, Russel's viper and saw-scaled viper. It is reconstituted by adding 10 ml. of distilled water. A sensitivity test is performed by injecting 0.02-0.1 ml. of 1 : 10 diluted antivenom subcutaneously. If no reaction occurs within 30 min., 20-40 ml. is injected intravenously, very slowly (0.5-1 ml./min.) as the first dose and repeated thereafter, if necessary, every 3-4 hours upto a total of 100 ml., depending upon the severity of the case. In case of viper bite, some serum is injected around the site of the bite to prevent the development of gangrene. The antivenom serum may also be given intramuscularly or subcutaneously though the intravenous route is the preferred one.

The presence of allergy demands desensitization and administration of the antiserum in small, multiple doses. Allergic reactions and anaphylaxis may occur and they should be treated by the conventional methods. Antivenin is probably not effective against the toxin fixed to the tissues, nor can it reverse the organic damage caused by the toxin. In a very serious case, one may not wait for the sensitivity test but give the serum immediately. In such circumstances, it is advisable to use prophylactically adrenaline, an antihistaminic and a glucocorticoid simultaneously, and repeat them later, if needed, to protect the patient against allergic reactions.

PRINCIPLES OF TREATMENT OF TETANUS

(a) **Administration of antitoxin or immunoglobulin:** Antitoxin should be given as early as possible. After a preliminary test dose, the patient should be watched for 30 minutes. Therapeutically, a dose of 10,000-20,000 units is usually adequate.

If available, tetanus immune human globulin is preferred to the ATS. It is given intramuscularly in the dose of 3,000 to 6,000 units.

(b) **Control of convulsions:** This may be achieved by administration of drugs like paraldehyde, chlorpromazine, diazepam, promazine and short-acting barbiturates. Usually, diazepam given parenterally is preferred. It can also be given orally. An excess of chlorpromazine may aggravate the convulsions. Skeletal muscle relaxants acting centrally or peripherally have also been employed. Barbiturates should be avoided for fear of respiratory depression. These drugs are discussed elsewhere. Convulsions can be minimised by keeping the patient in a dark room free from noises. Some authorities recommend the use of tubocurarine or gallamine to produce skeletal muscle paralysis along with artificial respiration and sedation. The results of this therapy are equivocal. Moreover, such therapy is impracticable in countries with a high incidence of tetanus and lack of adequate nursing facilities.

(c) **Prevention of secondary infection:** Benzyl penicillin is administered intramuscularly in the daily dose of 1 to 2 mega units. Penicillin also destroys the tetanus bacilli in the wound.

(d) **Supportive therapy:** This consists of good nursing care, aspiration of secretions from the respiratory passage, frequent turning of the patient, maintenance of adequate nutrition by intravenous and if possible by intragastric route and prevention and prompt treatment of bed sores. Tracheostomy may be required in severe cases. Local treatment of the wound by excision, and removal of necrotic material to allow free drainage, are also important.

Hyperpyrexia due to severe muscular spasm can be treated by tepid sponging. A person who has recovered from tetanus is not immune and should be actively immunised with the toxoid before discharge.

IMMUNOSUPPRESSANTS

Drugs which are used to suppress the immunity are called immunosuppressants. Since immunity confers resistance to disease, the use of drugs for deliberately suppressing it appears odd at first sight. However, according to present concept, the ability of the body to recognize self from not-self or foreign, which is the basis of immunity, is liable to disorders leading to failure to recognize or to tolerate antigens produced by its own tissues. This may cause exacerbation of existing disease processes or even produce new ones called 'auto-immune diseases' e.g. rheumatoid arthritis. Immunosuppressant drugs can be useful in such diseases. They are also useful for preventing the rejection of organ transplants. The drugs used are:

(a) Those which act by general suppression of all immune responses e.g. cytotoxic drugs—Azathioprine, Cyclophosphamide, Methotrexate (See Chapter 55).

(b) Those which are specific suppressants of immune responses e.g. Antilymphocytic serum (ALS) and

(c) Those which reduce the unwanted reactions due to immune responses probably due to their anti-inflammatory actions, with only a partial suppressant effect e.g. corticosteroids, salicylates, phenylbutazone.

(a) **General suppressants:** These are cytotoxic drugs which act on the dividing cells. An immune response is associated with division of lymphoid cells and these drugs act by interfering with the dividing lymphoid cells in the body. They, however, are not specific and produce toxicity as they also affect the other rapidly dividing cells, as discussed in Chapter 55. Azathioprine (Imuran) is the most commonly employed compound. When used in daily maintenance doses of upto 3 mg. per kg. body weight it rarely causes serious side effects, if renal function is satisfactory. However, continuous prolonged immunosuppression with cytotoxic agents is associated with a number of hazards particularly increased susceptibility to infection and hence, is to be recommended only in special circumstances e.g. organ transplants.

It is imperative to ensure an adequate antibiotic cover during immunosuppression. Failure to take this precaution may result in a fatal secondary infection.

(b) **Antilymphocytic serum (ALS):** The serum or semipurified antilymphocytic globulin is obtained from horses immunized against human thymus, lymph node and spleen cells (lymphoid tissue). When administered intramuscularly in the dose of 1000 units per kg. (1 to 5 ml. of the serum), along with other immunosuppressants like azathioprine and corticosteroids, in patients undergoing renal homotransplantation, it enables a considerable reduction in the dose of the other immunosuppressants. It, however, is not a substitute for these drugs.

Specific antithymuscytic globulin is obtained by injecting into horses, T cells from the thymus glands of children undergoing open heart surgery. The T cells are more vulnerable to ALS which depletes the thymus dependent areas of lymphoid tissue, the lymphocytes being replaced by histiocytes. ALS is of benefit during bone marrow transplantation and in the treatment of certain rejection crises.

The adverse effects reported include pain and induration at the site of injection, fever, occasionally anaphylactic response and thrombocytopenia. An increased incidence of malignant tumors like lymphomas has been reported in patients receiving it intravenously, repeatedly.

(c) **Corticosteroids:** See Chapter 60.

IMMUNOSTIMULANTS

The use of variety of agents to enhance immunological and nonspecific host defences and thus to modify the defences favourably is an exciting development in immuno-pharmacology. Such agents may act by increasing the humoral antibody responses, by enhancing the phagocytic activity of macrophages or by modifying the cell-mediated immune-responses.

Drugs like amantadine and tilorane stimulate the humoral immune system. The role of BCG vaccine in strengthening the immune defence mechanisms is discussed in Chapter 47. Nonspecific immunostimulation with BCG has been used along with the conventional therapy in treatment of leukemias, melanoma and lung carcinoma with some beneficial results. An anthelmintic drug levamisole also possesses immunotropic properties and has been shown to help in restoring the efficiency of host defence mechanisms. The drug has been used in the dose of 150 mg. orally for three consecutive days, given once a fortnight for 2-3 months, in the management of recurrent aphthous stomatitis, recurrent herpes infections, recurrent infections of skin and respiratory tract, with promising results. Larger doses (150-750 mg. three times weekly) have been used in the treatment of malignancies. The drug may cause gastrointestinal disturbances, headache and granulocytopenia. Levamisole probably acts by augmenting cellular responses. It restores or augments cutaneous-delayed hypersensitive reactions in anergic (state of immunologic deficiency) patients with cancer. Like BCG and clofazimine its effect is associated with enhanced phagocytic activity of the macrophages. Immunostimulant therapy is still in experimental stage and further development of safer and pharmacologically active immunostimulants is awaited. (For levamisole see l-Tetramisole, Chapter 54).

71 Radioactive Isotopes and Biological Effects of Radiation

A radioisotope of an element may be defined as a special kind of atom which has the physical property of giving out radiations. 'Isotope' means 'same place' and implies that these have the same place in the Mendeleev periodic table of the chemical elements. The radioactive isotope (radioisotope), therefore, would behave in the same way both chemically and metabolically as the stable element with the additional advantage of giving radiations which can be detected or can be used to destroy the tissue. Thus, used in tracer doses, the distribution, uptake and metabolic fate of such a radioisotope or a labelled compound can easily be studied.

Structure of an atom: If one splits a small amount of homogenous matter, say sodium chloride, the smallest particle of such a compound that retains the chemical properties of the bulk material is called the *molecule*; while the smallest particle of an element in it (sodium and chloride) is known as an *atom*. Thus, each molecule of sodium chloride contains one atom of sodium and one of chlorine. An atom is made up of a central core called the nucleus, surrounded by a cloud of electrons moving round the nucleus in well-defined orbits. The nucleus has a positive charge while the electrons have an equivalent negative charge so that the complete atom is electrically neutral. The atom is thus mainly an empty space, but retains its shape and volumetric displacement by means of its strong internal electric fields. For a given atom, there could be many orbits, each orbit usually containing two or more electrons. Orbits are grouped to form a shell each of which is characterised by a definite binding energy. The innermost shell is called K shell followed by L, M, N and O shells. The movement of electrons between innermost shells causes the production of x-rays, while their movements in outer shells are associated with the production of light. Electrons in outermost shells are valency electrons and take part in chemical combinations.

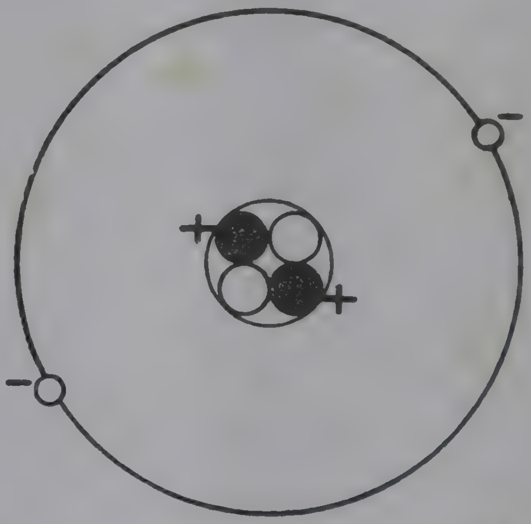


Fig. 71.1: Structure of an atom of helium, showing two protons, two neutrons and two electrons.

The phenomenon of radioactivity is associated with changes in the nucleus which consists of closely packed group of individual particles called 'protons' and 'neutrons' (Fig. 71.1). A proton is a positively charged particle with a definite mass. A neutron has about the same size and mass as the proton and is very much similar but has no charge; it is capable of changing itself into proton and vice versa. Since an atom is electrically neutral, the total positive charges on the nucleus equal the total negative charges of the orbital electrons. This number of protons is called the *atomic number* (Z) of an atom and it determines the place of the element in the periodic table. It is written as a subscript to the species symbol of the atom. Since electrons have negligible mass, the nucleus of an element determines its mass. The *mass number* (A) of an atom, therefore, is the total of number of protons (Z) and neutrons (N) in the nucleus. The chemical atomic weight (M) is the mass of one neutral atom relative to a particular standard (^{12}Carbon atom). The mass number A of the nuclear species is written as a superscript either to the left or right. Thus, the stable potassium can be written as ^{39}K or K^{39}.

What is radioactivity: The ratio of neutrons to protons in a nucleus of a given element may vary due to variations in the number of neutrons. Thus, most of the oxygen nuclei contain 16 particles 8 of which are neutrons. However, a few oxygen nuclei may contain 17 or 18 particles. Since an atom is electrically neutral and the number of electrons do not change, the number of protons in all these oxygen nuclei remains the same. Chemically, all these atoms with different atomic weights would behave like oxygen since the chemical properties are decided by the number and configuration of the electrons. In different isotopes of an element, therefore, the number of protons (Z) remains the same but the number of neutrons (N) and the mass number (A) differ. Some of these ratios of protons to neutrons give stability to the nucleus and the isotope is then referred to as a 'stable' isotope; while other ratios lead to instability. An unstable nucleus has excess of energy and it undergoes spontaneous transformation of the number of protons or neutrons or of their internal arrangement, in order to achieve stability. During this process, the excess of energy is given out in the form of radioactivity. Such isotopes are called radioactive isotopes (radioisotopes). Radioactive isotopes may exist in nature or can be prepared artificially by bombarding the stable elements with various atomic projectiles in a nuclear reactor or with a cyclotron. Short-lived radioisotopes such as ^{99m}Tc and ^{113m}I can conveniently be eluted in the laboratory from generator-produced short half-life radionuclides ^{99}Mo and ^{113}Sn respectively.

Nature of radioactivity: There are five different types of transformations which can take place within the nucleus resulting into various types of radioactivity. These are:

(a) **Alpha rays:** These are, in fact, swiftly moving particles of helium nucleus containing two protons and two neutrons (Fig. 71.1). They have a positive charge and a definite mass.

(b) **Beta rays:** These are high speed electrons with negligible mass. The commoner types have negative charge and are called 'negatrons' while some particles have positive charge and are called 'positrons'. Both these particles are otherwise similar.

(c) **Gamma rays:** These are electromagnetic waves produced by the radioisotope during the process of achieving ground level.

The gamma ray emitting radioisotope has its characteristic gamma ray spectrum analogous to the atomic spectra in the region of visible light. By noting this spectrum by means of a gamma ray spectrometer one can identify the isotope.

(d) **Electron capture:** In this process, a nuclear proton captures an electron from the innermost orbit and becomes a neutron. The atomic number is reduced by one. Rearrangement of electrons which follows such "electron capture" is accompanied by emission of characteristic x-rays.

(e) **Isomeric transition:** In this process, there is emission of gamma rays with a reduction in the energy level of the nucleus but without a change in the number of protons and neutrons in it.

Heavy nuclides like Uranium-238 undergo a change by spontaneous nuclear fission.

Unit of radioactivity: Since radioisotopes act because of their physical property of giving out radiation, the unit of radioactivity is based, not on the mass of the element, but on the rate of disintegrations per second. Thus, Curie (C) is defined as 3.7×10^{10} disintegrating nuclei per second. One Curie=1,000 millicuries and one milli-curie = 1,000 microcuries. During the process of disintegration, the isotope undergoes transformation, loses its activity (decays) and gives a decay product. Thus, radiogold-198, radiocobalt-60 and radiopotassium-42, during their decay to ground level, get converted into stable mercury, nickel and calcium respectively.

The Curie unit does not give an idea about the effect of a radioisotope on the tissues in terms of energy dissipated; it simply expresses the activity based on the nuclear changes at the origin of the radiation. In order to express the radiation effect on the tissues, units like 'Roentgen', or more commonly 'rad' are used. The 'rad' (r) expresses the dosage to the tissue in terms of energy dissipated and one rad is equivalent to 100 ergs of energy absorbed per 1 g. of tissue. A rem of radiation is that absorbed dose which produces in a given tissue the same biological effect as one rad of x-rays.

Properties of radioisotopes:

(a) **Penetrating ability:** Radiations given out can travel through or penetrate the matter. Alpha particles have poor penetrability while the beta particles can penetrate only a few (4-5) millimeters in the soft tissue. The gamma rays, however, can travel much farther and penetrate deeper into the tissues. Thus, from a pot containing a radioisotope emitting alpha, beta and gammas, even a thin paper will block the alphas and a 3-4 mm. thick aluminium plate the betas, but even a thick lead block may not completely cut off the escape of gammas (Fig. 71.2). Alpha radiations, therefore, cannot penetrate the skin and are not of medical interest except for the radiation hazard involved when certain long lived alpha emitting isotopes get fixed in the bones. The beta and gamma emissions, however, are useful both for diagnostic and therapeutic purposes. Gamma emitters are more suitable for the diagnostic purposes, because, after the administration of a tracer dose, it is easy to measure the body activity by measuring the radiation coming out of the body. Thus, radioisotope uptake by such tissues as thyroid, spleen, liver and bones can easily be studied *in vivo*. Further, tissue and fluid radioactivity can also be measured *in vitro* without any special processing. Gamma radiation, however, is not so useful for internal therapeutic purposes, because due to its penetrability, it would either escape without much effect or depending upon the energy, may cause damage resembling total body irradiation, even if the isotope is well localized. It can be used in therapeutics only as a beam directed towards the tissue from the source outside the body, as with radiocobalt units.

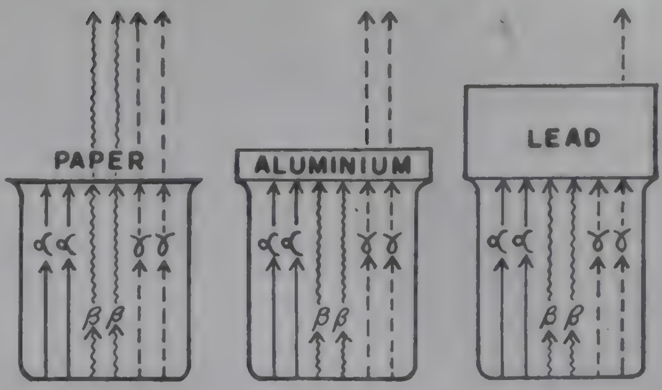


Fig. 71.2: Penetrating ability of alpha, beta and gamma radiations.

In vivo measurement of beta emissions is difficult because of their absorption within the tissues. Even in *in vitro* studies, much of the energy due to soft beta particles is absorbed within the test samples like blood, tissue or urine and may not reach the measuring device unless a special technic is used. Hence, beta emitting isotopes are not so useful for diagnostic studies but are of great importance for destroying the specific tissue selectively, because their activity is strictly limited to the area occupied by them.

(b) **Radioactive decay:** Unlike the ordinary therapeutic drugs, radioisotopes do not have an expiry date, but they are continuously losing their activity. Thus, 100 mc. of radiosodium-24, after 15 hours, will not be 100 mc. but 50 mc. This loss of radioactivity (decay) for a given isotope occurs in a predictable and unchangeable manner in a logarithmic fashion. The time taken for reduction of the activity to half of its zero-hour value is known as *physical half life* of that isotope. Thus, 100 mc. of an isotope with a half life of one day, would be 50 mc. after 24 hours, 25 mc. after 48 hours and 12.5 mc. after 72 hours and so on. The radioactivity of the isotope at a given time can be calculated by the formula:

$$\text{Present activity} = \frac{Ao}{2^m} \text{ where } Ao \text{ is}$$

the activity at zero-hour and m = number of half lives. Finally, the activity becomes so much less that it can no more be differentiated from the ever present natural 'background' radioactivity.

The amount of radiation delivered to the body varies directly with the half life of the isotope. Hence, other factors like type of radiation, energies and biological retention being equal, a radioisotope with a long half life will deliver greater radiation dosage to the tissue. This is particularly important if the element shows the tendency for cumulation in specific tissue.

The time taken by the element to reduce its body concentration to half of that administered is known as *'the biological half life'*. The *'effective half life'* of an isotope in a tissue not only depends upon its physical half life but also on the metabolism of that element/compound in the body (Biological half life). It is possible that an isotope with a very long physical half-life gets metabolised so rapidly that its biological half-life is very short, making its use much less hazardous. Thus, labelled compounds using carbon-14 with half-life of 5,760 years may not be so dangerous as strontium-90 with half-life of 28 years, as the former is rapidly metabolized and eliminated by the body within less than one day while the latter tends to get retained in the bones.

(c) **Ionization:** When a charged particle such as alpha or beta passes close to other atoms, electrostatic force operates between it and the orbital electrons of other atoms which lie along the path. If the particle passes close enough, one of the electrons may acquire sufficient energy to escape from the atom. This process is called ionization. The atom having lost one electron has a positive charge and, together with the electron, forms an ion pair. This ionization is mainly responsible for the biological effects of radiation and it forms the basis for the measurement of radioactivity with detectors like Geiger Muller (G.M.) counters. Gamma rays and neutrons being without any charge do not cause ionization directly. Gamma rays interact with the matter by producing secondary electrons; these secondary electrons behave exactly like beta rays.

(d) **Photographic effect:** All varieties of ionizing radiations blacken sensitive photographic paper when they reach it. This is made use of in the technique of autoradiography.

(e) **Calorigenic effect:** The temperature of a tissue is raised infinitesimally when it absorbs any form of ionizing radiation.

(f) **Chemical effect:** Certain chemicals in solution undergo oxidation, reduction or a colour change when exposed to ionizing radiations.

(g) **Photoelectric effect:** When gamma rays and x-rays fall upon certain chemicals, the latter emit energy in the form of 'light flashes'. Such chemicals are known as 'phosphors' and this phenomenon, called 'photoelectric effect', is utilized in the techniques of fluoroscopy and gamma ray counting by scintillation counting.

Tissue distribution and dosage: Radioisotopes can be administered as 'pure', where all the atoms are radioactive (carrier free) or mixed with some stable atoms of the same element (with carrier); the stable atoms are then called as 'carrier'. Thus, radioiodine is usually given as 'carrier free' while an isotope like radiogold is used diluted with the stable carrier. The addition of a carrier increases the total weight of the element and reduces the radioactivity per unit mass in mg. It is necessary, therefore, to mention the dose of the radioisotope as 'with or without a carrier'. It must be realised that an extremely small amount of a carrier-free isotope can have tremendously large dose of radioactivity.

The amount of radioactivity as a milli or microcurie per unit weight of the element or chemical compound is called 'specific activity'. A sample with large carrier will thus have a 'low specific activity' while that without a carrier will have 'high specific activity'.

The distribution of a radioisotope in the body usually follows the body distribution of its stable isotope, e.g. radio-sodium distributes itself according to stable body sodium and thus remains essentially extracellular in contrast to radiopotassium. This is because the body is unable to distinguish between radioactive and non-radioactive atoms. The radiation dose to the tissues will, therefore, be decided by the selective distribution, nature of the radioactivity and the metabolism of the radioisotope used. While considering the tissue dosage, one has to know both the *radiation dose* and the *dose rate.* The former gives an idea about the total energy absorbed while the latter gives the rate of absorption of the energy; this is often compared to total mileage reading and the speed indication on a speedometer of a car, respectively. The former is cumulative while the latter indicates the rate at which the car is speeding. Sudden large radiation dose can produce extensive damage as compared to the same total dose received over a prolonged period.

Detection of radioactivity: Radioactivity can be detected by various devices based on the following principles:

(1) The ionization of gases e.g. in proportional counters and G.M. counters.

(2) By counting 'scintillations' or 'flashes of light' produced by the gamma emitters in certain 'phosphors' (fluorescent material) e.g. in scintillation counter. This effect can also be recorded on a paper as in a scintiscanner to produce a scintiscan, or photographed by a gamma-camera showing the distribution of the isotope.

(3) By noting the blackening effect produced by the isotope on the photographic sensitive plate as in autoradiography.

The details of these methods are beyond the scope of this book.

Uses of radioisotopes in medicine: Radioisotopes are now extensively used in various branches of medicine for diagnostic, research and therapeutic purposes. The common uses of isotopes are:

I. **Haematology:**

(a) Measurement of blood volume, red cell survival, gastrointestinal blood loss by using red cells labelled with Chromium-51.

(b) Iron absorption, erythropoiesis and iron kinetics by using ^{59}Fe (iron).

(c) Vitamin B_{12} absorption studies with radiocobalt (^{57}Co) labelled B_{12}; folic acid absorption studies by using tritiated (^{3}H) folic acid.

II. **Chemical Pathology:**

(a) Studies on sodium, potassium, water and chloride metabolism using ^{24}NaCl, ^{42}KCl, tritiated water and radio bromide.

(b) Plasma protein metabolism using ^{131}I-human serum albumin; amino acid metabolism with ^{14}C or ^{35}S labelled amino acids.

(c) Fat absorption studies by using labelled ^{131}I-triolein and oleic acid.

(d) Calcium kinetics by using Calcium-47.

III. **Cardiovascular System:**

(a) Pulmonary and cerebral blood flow by using ^{85}Krypton.

(b) Cardiac output by using ^{131}I-human serum albumin (RIHSA).

IV. **Thyroid:**

(a) ^{131}I and ^{132}I uptake studies.

(b) Localization of thyroid tissue by using the same isotopes (Fig. 71.3).

V. **Urinary System:**

(a) Kidney localization by ^{203}Hg labelled chlormerodrin.

(b) Renal clearance studies by using ^{131}I-sodium iodohippurate.

VI. **Tissue Scanning:**

^{131}I and ^{99m}Tc for thyroid scanning; Indium-113-m for liver, lung, brain, kidney and bone marrow scanning; Technetium-99-m for liver, brain and spleen scanning; 75-

Selenomethionine for parathyroid and pancreas scanning and macro-aggregated RIHSA (MAA-^{131}I) for lung scanning.

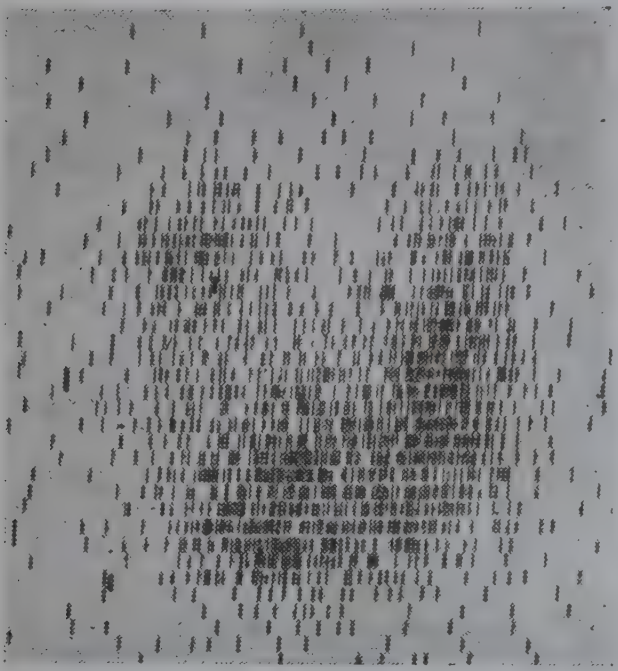


Fig. 71.3: Thyroid Scan, showing a low uptake area.

VII. **In assay procedures:** For biologicals and drugs e.g. radioimmunoassay.

VIII. **For Therapy:**

(a) ^{131}I for thyrotoxicosis and thyroid carcinoma.

(b) Radiogold (^{192}Au) and Cobalt-60 for the treatment of certain malignancies and secondaries.

(c) ^{32}P in the treatment of polycythemia vera.

(d) Yttrium-90 for radiation hypophysectomy.

(e) Tantallum-182 for carcinoma of bladder.

Apart from these, almost every compound can be labelled with a radioisotope and its metabolism studied *in vivo.* Radioisotopes are now used in 'radio-immune assay' procedures, used for various hormonal estimations such as insulin, ACTH, growth hormone and gonadotropins. Such assays are very sensitive and precise as compared to conventional chemical or biological procedures.

BIOLOGICAL EFFECTS OF RADIATION

Studies on the biological effects of ionizing radiation started very shortly after the discovery of x-rays by Roentgen in December 1895. Very soon, it was appreciated that unlike chemical agents, the cellular penetration of which is prevented by natural cellular barriers, the radiation can penetrate the cells and deposit its energy within them in a random fashion, leading to radiation damage. All of us are exposed to a certain amount of natural radiation in the environment e.g. cosmic rays, natural radioisotopes like ^{40}K, terrestrial radiation due to increased amount of radio-active material in the soil as from the monazite sands of Kerala. To this is added the man-made radiation such as that from discharge tubes of television sets and luminous markings on watches. Such a background radiation, so far, has not been shown to produce any harmful effects. However, individuals can receive considerable amounts of radiation following fluoroscopy and repeated x-ray procedures. The testing of various nuclear weapons since the introduction of nuclear energy 25 years ago has increased the background radiation significantly in recent years. Further, it is now possible that following the detonation of some such weapons, mankind can be exposed to radiations equivalent to those which might be produced by several hundred tons of radium.

The first atomic bomb was exploded on 6th August 1945 in Hiroshima, Japan, where about 63,000 people were killed. Three days later, another atom bomb was dropped on Nagasaki where about 40,000 people lost their lives. Many of these casualties were due to acute radiation damage. Since then, bombs with far more destructive capacities have been developed. The kilo-ton detonations are usually fission devices. Apart from the localised damage following their explosion, large amounts of earth soil are fused with the fission products such as ^{131}I, ^{90}Sr and ^{137}Cs and carried away by the wind. The radioactivity from such devices, thus, may get spread over hundreds of miles from the site of detonation, leading to high background radiation. The large mega-ton detonations derive their energy primarily from fusion of atoms; this process does not produce fission products. The limited amounts of fission products produced with such detonations are due to a small fission device usually employed to trigger the fusion reaction. However, the fusion reaction releases large number of neutrons which interact with various atoms in the environment and convert them into radioactive isotopes. Thus, gaseous Carbon-14 with half life of 5,760 years is produced. The tremendous amount of energy produced during the mega-ton detonation forces the fireball and typical 'mushroom cloud' to such heights that the radioactive material is taken up to stratosphere from where it can get very widely distributed over thousands of miles, the deposition of which is facilitated by rainfall. Crops grown on such contaminated soil will thus have high concentrations of such materials as ^{90}Sr (half life 28 years), ^{137}Cs (half life 30 years) or ^{131}I. It is this type of radiation, with potentialities of causing inconceivable damage to the human race and its environment, which is causing great concern. Such radiation not only causes immediate toxic effects but can also produce serious delayed changes. The problem of radiation exposure due to internally deposited radioisotopes can be well illustrated by the following example. The main plant life near the Arctic Circle is lichens, which unlike the temperate plants, survive for many decades. These plants accumulate long half-life fall-out products from atomic bomb tests. Since lichens are the principle food stuff for caribou and reindeer, the radioactive material gets into these animals, whose meat forms the main food for the Eskimos. Through such food chain, Eskimos have already accumulated considerable amounts of Cesium-137.

The radiations that can produce damage are the alpha and beta particles, neutrons, protons, x-rays and gamma rays. The damage produced depends upon the susceptibility of the tissues, the dose rate and the penetrating power of the radiation. The radio-sensitivity of the tissue varies from tissue to tissue and differs in various species. Thus, the radiation dose necessary to kill fifty per cent of sample population (LD50) is, 300,000 r for paramecia, 100,000 r for amoeba, 60,000 r for fruit fly, 10,000 r for a snail, 700 r for a frog and anything between 200-1000 r for mammals. All mammalian cells are vulnerable to radiation damage, though their sensitivity may vary. In man irradiation of the whole body with a dose of 300-500 rads is usually fatal, but in the treatment of malignant tumours as much as 10,000 rads may be given to a small volume of tissue without serious effects.

Effect of ionizing radiations: Corpuscular radiations such as beta rays and protons directly cause ionization while gamma rays and x-rays first eject fast electrons from atoms within the cell, which, in turn, lose their energy by interactions with other molecules in the cell causing ionizations and excitations. Although much of the energy absorbed by irradiated cells causes excitation, most of this energy does not produce chemical reactions and is eventually dissipated as heat. It is the ionization which causes disruption of molecules and the release of highly reactive free ions. Two important theories have been postulated to explain the cellular damage produced by radiation. The target theory explains this purely on the basis of the physical nature of the radiation. According to this theory, "the cell contains a critical site or target and a single ionizing event or hit within this target will inactivate the cell; a hit outside the critical site would have no effect". According to indirect theory, however, the ionization event may involve other small molecules like water within the cell and after some chemical reactions, the energy may then be transferred to the target molecule leading to its inactivation. Thus, ionization of water produces hydrogen ($H+$), hydroxyl (OH^-) and perhydroxyl free radicles. These are highly unstable and, therefore, very reactive. These react with each other and with neighbouring organic molecules to produce a variety of secondary chemical substances such as peroxides which are highly injurious to the cell. Since roughly 80 per cent of the mammalian cell is water, it is probable that most of the cellular radiation damage is mediated by aqueous-free radicles. Although the injury to several different sites in the cell may be responsible for the lethal effect, the damage to DNA probably plays a key role in cellular radiosensitivity.

Following irradiation, cell death may occur due to mitotic inhibition and reproductive failure which is, by far, the most important mechanism of cell death. In a few instances, degeneration occurs immediately, irrespective of the stage in the cell cycle. In the former case, the irradiated cells show no visible damage but degenerate eventually.

Various substances have been shown to sensitize the cells to irradiation. Among these, oxygen is perhaps the most important. Thus, the radiosensitivity of cells rises rapidly from the anoxic state and becomes maximum at an oxygen tension (pO_2) of about 20-30 mm. of mercury. Hyperbaric oxygen is sometimes used to increase the radiosensitivity in patients undergoing radiotherapy for malignant neoplasm. The other radiosensitizers include nitric oxide, iodoacetamide, methotrexate and halogenated pyrimidine analogues such as 5-bromodeoxyuridine and 5-iododeoxyuridine. These, however, are not of much clinical significance.

For practical purposes, the damage caused by irradiation is usually divided into that affecting the cells of the skin, the mucous membrane of the intestines, the bone marrow, liver etc. and known as *'somatic effect'*, and that concerned with the 'hereditary patterns' of the species from one generation to another and known as *'genetic effects'*.

Acute radiation effects: The whole body irradiation with a dose of more than 100 rads may cause symptoms of acute radiation syndrome in man. The LD_{50} for man is not known but is believed to be about 450-500 rads. Large doses may cause immediate death due to injury to the brain (hyperacute reaction).

The acute radiation syndrome is characterized by severe nausea, vomiting and prostration. Within a few hours, diarrhoea may develop; if the dose is less than 500 rads, it may occur after 3 to 4 weeks. It is due to necrosis and ulceration of the gastro-intestinal tract and may be accompanied by bleeding. Large doses cause high fever which is a bad prognostic sign. Fever also occurs later due to infection. Various blood elements such as red cells, granulocytes, lymphocytes and platelets are markedly decreased and this may cause anemia, bleeding from various sites and increased bruisability. There is a general deterioration of health, and death may ensue within 2 to 3 weeks, after a heavy exposure. Radiation decreases antibody formation and lowers the body resistance, and many delayed deaths are due to infection. In mild cases, the interval between exposure and initial symptoms is longer, blood changes are less marked and recovery can occur in 90 per cent of the subjects.

There is no specific drug at present which can effectively counter the effects of radiation without causing toxicity, and the treatment of acute radiation syndrome is purely symptomatic. It includes excellent nursing, maintenance of optimal nutrition and fluid balance, blood transfusion, antibiotic therapy and general symptomatic care. Homologus bone marrow transfusion has been used but is of doubtful value.

Delayed effects of radiation: Death from acute radiation syndrome rarely occurs after 6-8 weeks in man. However, such an acute exposure to non-lethal radiation and chronic exposure to low level radiation can give rise to certain delayed effects. These are:

(a) *Ageing effect*: Radiation can accelerate the physical process of ageing and shorten the life span. There is an early greying of the hair, epilation and early development of vascular and degenerative changes and lenticular cataracts. These effects can be clearly demonstrated in animals but convincing evidence in humans is lacking.

(b) *Induction of neoplasms*: Carcinoma of the skin following radiation, osteogenic sarcoma following radium deposition in bones and lung cancer following the inhalation of radon in uranium mine workers are well known. Evidence from the atomic explosions in Japan clearly indicates that ionizing radiation can increase the incidence of leukemia, Hodgkin's disease and thyroid cancer. There is some evidence to suggest that the incidence of leukemia in children exposed to radiation *in utero*, during the diagnostic radiological procedures in pregnancy and in patients with rheumatoid spondylitis treated with radiation, is also high. It is estimated that the exposure of foetus to radiation increases the risk of cancer during the first ten years of life by about 40 per cent over the unexposed children. Although the smallest dose that can induce neoplastic changes is not yet established, it is safer to assume that even a small dose may cause some damage and hence, should be avoided.

(c) *Effect on gonads*: Single large doses to gonads can cause sterility, and increased incidence of azoospermia or hypospermia in males exposed to radiation has been reported; the results of chronic total body radiation, however, are inconclusive.

(d) *Chromosomal damage*: Radiation is known to cause genetic damage in cells, and repeated irradiation of cultured cells has produced resistant cell lines with altered chromosome numbers. Only a few rads of exposure can induce chromosomal aberrations in human leukocytes, and such changes can persist for many years. That x-rays can increase the frequency of mutations in the fruit-fly, Drosophila, was shown by H. J. Muller in 1927. It is now known that other types of radiation like gamma and ultraviolet radiation can also alter the mutation rate. Evidence in lower animals indicates that such chromosomal mutation may lead to decreased fertility and sterility while gene mutations can cause offsprings with structural defects. Recent studies in animals indicate that low levels of radiation are not so deleterious as a single high dose of brief duration. No increase in the incidence of abnormalities has so far been observed in the offspring of the population exposed to radiation from atomic bombs or in the population from Kerala, India, where the average level of radiation is as high as 2800 mrems per year. However, the possibility of inducing mutations is well established and at present, no amount of radiation can be considered as safe from this point of view. The important point to remember is that induced mutations may harm individuals in future generations of man. Since the sensitivity is probably maximum in human embryos during 2-6 weeks of development, pelvic irradiation in women of childbearing age should be limited to the ten day period after the onset of menstruation. It may be noted, however, that not all mutations are deleterious both in the homozygous form and the heterozygous state.

Radiation protection: The treatment of radiation damage, once established, is disappointing. It is important, therefore, to avoid radiation exposure as far as possible. The radiation dose received from the radioactive material varies inversely with the square of the distance. Hence, even doubling the distance between the source and the individual will reduce the dose received to one-fourth. Beta radiations can be cut out by thick glass or perspex but even a thick lead apron may not completely protect the subject from the gamma radiations. Proper shielding, however, plays an important role in radiological protection. Use of personal monitoring devices like film badges containing sensitive plates, which record the effects of various radiations, can give some idea regarding the dose that the individual has received. This would help to estimate the cumulative dose received during a specific period. Clinically, regular blood counts may be done in individuals working with radiation, for the detection of abnormal blood picture.

Various radioprotective agents have been studied experimentally. One group offers the protection only *in vivo,* primarily by producing systemic hypoxia, and includes such diverse agents like histamine, cyanides, catecholamines, p-aminopropiophenone, some anaesthetic agents and tryptamine. The group of drugs which can protect both *in vivo* and *in vitro* include cystamine, mercaptoethylamine, cysteine, glutathione and 2-mercaptoethylguanidine; these agents usually contain a free or potential sulfhydryl (SH) group at one end and a basic amine or guanidine group at the other. Unfortunately, the most effective chemical radioprotective drugs of these are highly toxic in effective doses and hence, are not of much clinical significance. Chelating agent like EDTA may be used for removing radioelements from the soft tissues; it is particularly effective for plutonium and rare earth fission products. Zirconium citrate can also minimize the tissue deposition of radioelement like plutonium.

In order to avoid the possible radiation hazards in practice, one should weigh the possible risks from radiation exposure against the value of diagnostic tests in a given subject. In most cases, the risk is small. It is much safer to have an x-ray done rather than repeated fluoroscopic examinations, particularly in children. Protection against internal exposure can be ascertained by avoiding ingestion or inhalation of the contaminated material. This, however, is not always easy since ordinarily it is not possible to sense a radioactive isotope.

APPENDIX A: Guide to Further Reading

Although a large number of monographs, reviews, original papers and text-books were consulted during the preparation of this text-book, only a selected list for further reading is given below. This, obviously, does not detract from the extensive and high-quality references available on the various topics.

Alstead S. and Girdwood R. H. (Ed): Textbook of Medical Treatment, 13th Edition, 1974, E. and S. Livingstone Ltd., London, U.K.

Avery G. S. (Ed.): Drug Treatment, 1st Edition, 1976, ADIS Press, Sydney.

AMA Drug Evaluations 1975, (3rd Ed.): Publishing Sciences Group Inc., U.S.A.

Blachly P. H. (9d.): Drug Abuse, 1970, C. C. Thomas U.S.A.

Beckman H. (Ed.): The Yearbook of Drug Therapy, Yearbook Medical Publishers, Chicago, U.S.A.

Black D. A. K.: Essentials of Fluid Balance, 2nd edition, 1968, Blackwell Scientific Publications Ltd., Oxford, U.K.

Braude A. I.: Antimicrobial Drug Therapy — Vol. VIII in the series Major Problems in Internal Medicine, W. B. Saunders, London, 1976.

Cluff L. E., Caranasos G. J. and Stewart R. B.: Clinical Problems with Drugs Vol. V in the series Major Problems in Internal Medicine, W.B. Saunders Co., London. 1975.

Dash C. H. and Jones H. E. H.: Mechanisms in Drug Allergy 1972, Churchill-Livingstone, U.K.

Fisher J. W. (Ed.): Renal Pharmacology, 1971, Meredith Corp., U.S.A.

Garrod L. P. and O'Grady F.: Antibiotics and Chemotherapy, 4th Edition, 1973, E. and S. Livingstone, London, U.K.

Goldstein A., Aronow L. and Kalman S.: Principles of Drug Action, 2nd Ed., 1974, John Wiley & Sons Inc.

Goodman L. S. and Gilman A. (Ed.): The Pharmacological Basis of Therapeutics, 5th Edition, 1975. The Macmillan Company, New York, U.S.A.

Holmstedt B. and Liljestrand G.: Readings in Pharmacology, 1963, Pergamon Press, London.

Kalow W.: Pharmacogenetics—Heredity and the Response to Drugs, 1962, W. B. Saunders and Co., New York, U.S.A.

Krantz J. C.: Historical Medical Classics involving New Drugs 1974, William & Wilkins Co., U.S.A.

La Du B. N., Mandel W. G. and Way E. L.: Fundamentals of Drug Metabolism and Drug Disposition, 2nd Ed., 1972, Kothari Book Depot, Bombay.

Lasagna L. (Ed.): International Encyclopedia of Pharmacology and Therapeutics, Section 6, Vols. I and II, 1966, Pergamon Press, New York, U.S.A.

Lawrence D. R. (Ed.): Drugs, Development and Use, Brit. Med. Bull., 26: No. 3, 1970.

Lawrence D. R. and Bacharach A. L. (Ed.): Evaluation of Drug Activities, Pharmacometrics, 1964, Academic Press, London, U.K.

Melmon K. L. and Morrelli H. F. (Ed.): Clinical Pharmacology, 1972, The Macmillan Co., New York.

Meyler L. and Herxheimer A.: Side-effects of Drug 1968-71, Excerpta Medica Foundation, Amsterdam.

Modell W. (Ed.): Drugs of Choice 1972-73, Mosby and Company, Saint Louis, U.S.A.

Nodine J. M. and Siegler P. E. (Ed.): Animal and Clinical Pharmacologic Techniques in Drug Evaluation, Vol. I, 1964, Yearbook Medical Publishers Inc., Chicago, U.S.A.

Notari, D.: Pharmacokinetics and Biopharmaceutics, 2nd Ed., 1977, Dekker Publishers.

Onesti G., Kim K. E. and Moyer J. H. (Ed.): Hypertension — Mechanism and Management 1973, Grune a Stratton, N. Y.

Paranjpe A. S.: A History of Pharmacology, Maharashtra Medical Journal 1961-62.

Roitt, I. M.: Essential Immunology, 3rd Ed., 1977. Blackwell Scientific Publications, London.

Siegler P. E. and J. H. Mayer II. (Ed.): Animal and Clinical Pharmacologic Techniques in Drug Evaluation, Vol. 2, 1967, Yearbook Medical Publishers, Inc., Chicago, U.S.A.

Swarbrick J. (Ed.): Biopharmaceutics 1970, Lea & Febiger, Philadelphia.

Swarbrick J. (Ed.): Dosage Form, Design and Bioavailability 1973, Lea & Febiger, Philadelphia.

Swayer G. I. M. (Ed.): Control/of Human Fertility, Brit. Med. Bull, 26: No. 1, 1970.

Thomas J. A. and Mawhinney M. G.: Synopsis of Endocrine Pharmacology 1973, Univ. Park Press, Baltimore.

Wade O. L.: Adverse Reactions to Drugs, 1970, William Heinemann Medical Books Ltd., London.

Wolstenholme G. and Porter R. (Ed.): Drug Responses in Man 1967. A Ciba Symposium, J. & A. Churchill Ltd., London, U.K.

Apart from these, students may refer to the following journals for interesting articles, reviews, and symposia: British Medical Bulletin, New Eng. J. Medicine, British Medical Journal, The Lancet, Clinical Pharmacology and Therapeutics, Ann. Rev. Pharmacology, W.H.O. Technical Reports, Pharmacological Review, Drugs, British, J. Pharmacology, Ann. Internal Medicine and Prescriber's Journal.

APPENDIX B: List of Drugs included in B.P. 1973; addendum 1975.

N.B. This list does not include all the entries in B.P. i.c. = intracutaneous, i.m. = intramuscular, i.v. = intravenous, s.c. = subcutaneous, o. = oral, T or Tab. = tablet, Tr. = tincture, HCl = hydrochloride, p.d. = per day, div. = divided doses.

Official Drug		Dose
Acetarsol (Acetarsone)	:	50 to 250 mg. twice a day for 10 days.
Acetazolamide Tab.	:	Initial, 500 mg. Then 250 mg. every 6 hrs.
Acetomenaphthone Tab. (Menadione)	:	In the prophylaxis of neonatal haemmorrhage, 5 to 10 mg. daily for one week before delivery. In the preoperative treatment of obstructive jaundice, 10 to 20 mg. daily for one week. For other doses see page 378
Adrenaline Acid Tartrate, s.c.	:	0.4 to 1 mg.
Adrenaline Inj. 1:1000, s.c.	:	Single dose, 0.2 to 0.5 ml. In status asthmaticus and other allergies, 0.05 ml. per minute.
Allopurinol Tab.	:	0.2 to 0.3 g. p.d. div.
Aloes	:	0.1 to 0.3 g.
Alprenolol Inj.	:	By Slow i.v. 5-20 mg. at rate of 1 mg/min
Alprenolol Tab.	:	Initially 100-200 mg. daily Then upto 800 mg. p.d. div.
Aluminium Hydroxide Gel	:	7.5 to 15 ml., repeated as per case.
Aluminium Hydroxide Gel Dried	:	0.5 to 1 g., repeated as per case.
Aluminium Hydroxide Tab.	:	1-2 tab. repeated as necessary.
Amethocaine HCl	:	See text page 180.
Aminocaproic Acid	:	100 mg./kg. every 4-5 hours i.v. infusion.
Aminophylline Tab.	:	0.1 to 0.3 g., repeated as per case.
Aminophylline Inj., slow i.v.	:	0.25 to 0.5 g.
Amitriptyline HCl, i.m., i.v. o.	:	50 to 100 mg. p.d. div. Initial dose, 75 to 150 mg. p.d. div. Maintenance dose, 50 to 100 mg. p.d. div.
Amitriptyline Tab.	:	Initially 75 to 150 mg. p.d. div. Then 50 to 100 mg. p.d. div.
Ammoniated Mercury ointment, topical	:	2.5 per cent.
Ammonium Chloride	:	Before Mersalyl injection, 3 to 6 g. p.d. div.
Amodiaquine HCl	:	See page 604.
Amoxycillin Trihydrate, o.	:	0.75-4.5 g. p.d. div.
Amphetamine Sulphate Tab.	:	Morning and midday, 5 to 20 mg. p.d. div.
Amphotericin	:	Oral and Topical
Ampicillin and Ampicillin Trihydrate, o.,	:	2 to 6 g. p.d. div.
i.m.	:	1 to 3 g. p.d. div.
Amylobarbitone and Its Sodium Salt, o., i.m., s.c., i.v.	:	Hypnotic 100-200 mg. o. Sedative upto 600 mg. p.d. div.
Antazoline HCl, o.	:	100 to 300 mg. p.d. div.
Apomorphine HCl, s.c., i.m.	:	Emetic, 2 to 8 mg.
Ascorbic Acid (Vitamin C)	:	Prophylactic, 25 to 75 mg. p.d. Therapeutic, 250 mg. p.d. div. or more.
Aspirin	:	0.3 to 1 g., upto 4 g. p.d. div. In the treatment of acute rheumatism, 4 to 8 g. p.d. div.
Atropine Methonitrate	:	In congenital hypertrophic pyloric stenosis of infants, 0.2 to 0.6 mg. 30 minutes before feed.

Official Drug		Dose
Atropine Sulphate, o., s.c., i.m., i.v.	:	0.25 to 2.0 mg.
Atropine Eye Ointment, topical	:	1 per cent
Azathioprine Tab.	:	100 to 150 mg. daily.
Bacitracin zinc	:	Intestinal antiseptic, 100,000 to 150,000 units p.d. div.
Barbitone Sodium	:	Hypnotic, 0.3 to 0.6 g. Sedative, upto 900 mg. p.d. div.
Beclomethasone dipropionate	:	Topical
Belladonna Dry Ext, o.	:	15 to 60 mg.
Belladonna Tr.	:	0.5 to 2 ml.
Belladonna Prepared Herb	:	30 to 200 mg.
Bendrofluazide, o.	:	2.5 to 10 mg. daily.
Benzathine Penicillin, i.m.	:	Prophylactic, 0.9 g. every 2 to 3 weeks.
Benzhexol HCl	:	Initial, 2 mg., increasing gradually to 20 mg. p.d. div.
Benzocaine	:	See text page 180.
Benztropine Mesylate, o.	:	Initial, 0.5 mg. p.d. Subsequently, upto 6 mg., as per case.
Benzyl Benzoate, topical	:	25 per cent w/v.
Benzyl Penicillin, o., i.m., i.v.	:	0.5 to 3 g. p.d. div., i.m. i.v. 0.3—6 g. p.d. div.
Betamethasone, o.	:	0.5 to 5 mg. p.d. div.
Betamethasone Sodium Phosphate, i.v. o., i.m.	:	As above. Equivalent of 10 to 80 mg. div. of Betamethasone p.d. div. for acute adrenal insufficiency.
Betamethasone Valerate	:	Topical
Bethanidine sulphate	:	Initial 10-20 mg. p.d. div. Maintenance upto 200 mg. p.d. div.
Biperiden lactate	:	5 mg. i.m., i.v. upto 20 mg. p.d. div.
Bisacodyl, o., per rectum	:	5 to 10 mg. p.d.
Botulinum Antitoxin, i.c., i.m.	:	See page 849.
Bupivacaine HCl	:	Local anaesthetic
Bulsulphan Tab.	:	2 to 4 mg. daily. Maintenance, 0.5 to 2 mg. daily.
Butobarbitone Tab.	:	0.1 to 0.2 g.
Caffeine or Its Hydrate, o.	:	100 to 300 mg.
Calciferol (Vitamin D_2)	:	See page 796.
Calcium Amino Salicylate	:	10 to 15 g. p.d. div.
Calcium Carbonate, o.	:	1 to 5 g. repeated as per case.
Calcium Gluconate, o.	:	1 to 5 g. repeated if necessary.
10 per cent, i.m., i.v.	:	1 to 2 g.
Calcium Lactate, o.	:	1 to 5 g.
Camphor Liniment, topical	:	20 per cent w/w.
Capreomycin sulphate i.m.	:	1 mega-unit equiv. to 1 g. daily.
Carbachol, s.c.	:	0.25 to 0.5 mg.
Carbamazepine Tab.	:	0.2-1.2 g. p.d. div.
Carbenicillin Sodium	:	I.V. injection or infusion. The equivalent of 12-30 gms. of carbenicillin p.d. div. i.m. equivalent of 4 to 8 g. of carbenicillin p.d. div.
Carbenoxolone-Na	:	0.3 g. p.d. div. for one week. Then up to 150 mg. p.d.
Carbimazol Tab.	:	Controlling dose, 30 to 60 mg. p.d. div. Maintenance dose, 5 to 20 mg. daily.
Carbromal, o.	:	0.3 to 1 g.

Official Drug	Dose
Cascara Dry Ext.	100 to 300 mg.
Cascara Liquid Extract	2 to 5 ml.
Castor Oil	5 to 20 ml.
Cephalexin	1 to 4 g. p.d. div.
Cephaloridine, i.m.	0.5 to 1 g. p.d. div.
Cephalothin-Na, i.m., i.v.	2 to 6 g. p.d. div.
Chalk (Prepared Chalk, Creta)	1 to 5 g. repeated as per case.
Chloral Hydrate, o.	0.3 to 2 g.
Chlorambucil Tab.	Initial, 5 to 10 mg. daily. Maintenance, 2 to 4 mg. daily.
Chloramphenicol, o.	Child, 25 to 50 mg./kg. p.d. div Adult, 1.5 to 3 g. p.d. div.
Chlorcyclizine HCl, o.	50 to 200 mg. p.d. div.
Chlordiazepoxide HCl, o.	10 to 100 mg. p.d. div.
Chloroform Spirit	0.25 to 2 ml.
Chloroquin Phosphate, o., i.m., i.v	In malaria, see page 604. In hepatic Amoebiasis, see page 618. In lupus erythematosus and rheumatoid arthritis. 0.25 to 1.5 g. p.d. div.
Chloroquin Sulphate, o., i.m., i.v.	In malaria, see page 604. In lupus erythematosus, rheumatoid arthritis, 0.2 to 1.2 g. p.d. div. In hepatic amoebiasis, 0.4 to 0.8 g. p.d. div.
Chlorthiazide o.	0.5 to 2 g. daily.
Chlorotrianisene	In menopausal symptoms, 10 to 25 mg. p.d. for 30 days. For suppression of lactation, 40 to 50 mg. thrice daily for 4 days. In prostatic malignancy, 20 to 30 mg. p.d.
Chlorphenesin	Topical antifungal
Chlorpheniramine Maleate, o.,	4 to 16 mg. p.d. div.
i.m.	5 to 20 mg. as a single dose.
Chlorproguanil HCl, o.	20 mg. weekly as single dose.
Chlorpromazine HCl, o.,	Antiemetic, 25 to 50 mg. Psychiatric state, 75 to 800 mg. p.d. div.
i.m.	Antiemetic, psychiatric state, 25 to 50 mg.
Chlorpropamide, o.	250 to 500 mg. p.d.
Chlortetracycline HCl	1 to 3 g. p.d. div.
Chlorthalidone; o.	100 to 200 mg. p.d.
Choline Theophyllinate, o.	0.4 to 1.6 g. p.d. div.
Chorionic Gonadotropin, i.m.	500 to 5,000 units twice weekly.
Clioquinol (Iodochlorhydroxyquin), o	0.75 to 1.5 g. p.d. div.
Clofibrate	Upto 2 g. p.d. div.
Clomiphene Citrate	As per need
Cloxacillin Sodium, o., i.m.	1.5 to 3 g. p.d. div.
Cocaine HCl	See text page 181.
Cod Liver Oil (Ol. Morrhuae)	Prophylactic, not more than 10 ml. p.d.
Codeine Phosphate	10 to 60 mg.
Colchicine	Initial, 1 mg., followed 2 hrly. by 0.5 mg. until relief from pain or vomiting or diarrhoea results.
Colchicum Tr.	Upto 6 ml. p.d. div.
Colistin Sulphate, o.	9 to 18 megaunits p.d. div.
Colistin Sulphomethate Sodium, i.m., i.v. infusion	3 to 9 megaunits p.d. div.
Corticotrophin Injection (ACTH)	For maximal adrenal stimulation, 45 to 90 units

Official Drug	Dose
Material labelled "for intravenous use only"	according to the age of the patient, by slow infusion over 8 to 24 hrs.
Material labelled "for i.m. or s.c. use only"	As per need.
Corticotrophin Gelatin Injection, i.m. :	As per case.
Corticotrophin Zinc Hydroxide Inj. :	As per case.
Cortisone Acetate, o., i.m. :	50 to 400 mg. p.d. div. For replacement therapy after adrenalectomy, in Addison's disease, pan-hypopituitarism, 12.5 to 50 mg. daily.
Co-trimoxazole tab. :	2 to tabs. p.d. div.
Cyanocobalamin (Vit. B_{12}), i.m. :	See page 393.
Cyclizine HCl, o. :	25 to 50 mg., repeated as per case.
Cyclobarbitone Calcium Tab. :	0.2 to 0.4 g.
Cyclomethycaine Sulphate :	Topical anesthesia, 0.5 to 1 per cent.
Cyclopenthiazide, o. :	0.25 to 0.5 mg. p.d.
Cyclopentolate HCl, eye drops :	0.5 to 1 per cent.
Cyclophosphamide, o., i.v. :	100 to 150 mg. p.d.
Cycloserine, o. :	250 to 750 mg., p.d. div.
Cyproheptadine HCl, o. :	4 to 20 mg., p.d. div.
Dapsone Tab. :	See page 588.
De-methylchlortetracycline, o. :	0.6 to 1.8 g. p.d. div.
Deoxycortone Acetate, i.m. :	2 to 5 mg. p.d.
implantation :	100 to 400 mg.
Desferrioxamine Mesylate :	In children 2 g. i.m. and 5 g. orally after gastric lavage.
Desipramine HCl, o. :	Initial, 25 to 75 mg. single or div. Gradually increased to 200 mg. p.d. Maintenance, upto 150 mg. p.d. div.
Dexamethasone or Its Acetate, Sulphate :	0.5 to 10 mg. p.d. div.
Dexamphetamine Sulphate :	Morning and Mid-day, 5 to 20 mg., p.d. div.
Dextran '40' (Low Molecular Weight) inj., i.v. :	See page 359.
Dextran '70' :	See page 359.
Dextran '110' Inj., i.v. :	See page 359.
Dextromethorphan HBr, o. :	15 to 30 mg.
Dextromoramide Tartrate, o. :	5 mg., repeated as per case.
Dextropropoxyphene HCl or Napsylate, o. :	Upto 260 mg. p.d. div.
Dextrose Inj., i.v. :	5 per cent w/v.
Diamorphine HCl, i.m., s.c. :	5 to 10 mg.
Diazepam :	5 to 30 mg. p.d. div.
Diazoxide, o. :	150-1000 mg. p.d. div.
Inj. i.v. :	300 mg.
Dichloralphenazone, o. :	As hypnotic, 0.5 to 2 g. single dose.
Dichlorophene, o. :	Adult, 6 g. for two successive days, div. Child, 2 to 4 g. for two successive days, div.
Dichlorophenamide Tab. :	25 to 50 mg. 1 to 4 times daily.
Dicyclomine HCl, o. :	As parasympatholytic antispasmodic, 30 to 60 mg. p.d. div.
Dienoestrol Tab. :	In menopause, 0.5 to 5 mg. p.d. For suppression of lactation, 15 mg. thrice daily for 3 days followed by 15 mg. daily for 6 days. In carcinoma of prostate, 15 to 30 mg. p.d.
Diethyl Carbamazine Citrate :	0.15 to 0.5 g. p.d. div.
Prepared Digitalis and Prepared Digitalis Tab. : (10 units in 1 g.)	For rapid digitalisation, 1 to 1.5 g. Maintenance dose, 100 to 200 mg.
Digitoxin, o. :	See page 305.

Official Drug	Dose
Digoxin, o., i.m., slow i.v.	See page 305.
Dihydrocodeine tartrate	Oral, s.c. or I.M. 30-60 mg.
Dihydrotachysterol, o.	0.125 to 1.25 mg. p.d.
Diiodohydroxyquinoline	1 to 2 g. p.d. div. for 20 days.
Diloxanide Furoate Tab.	1.5 g. p.d. div. for 10 days or more.
Dimenhydrinate, o., i.m.	25 to 50 mg., repeated as per case.
Dimercaprol (B.A.L.), i.m.	See page 813.
Dimethisterone, o.	15 to 40 mg. p.d. div.
Diphenhydramine HCl, o.	50 to 200 mg. p.d. div.
i.m., i.v.	10 to 50 mg. single dose.
Dipipanone HCl, s.c., i.m.	25 to 50 mg.
Di-sodium Edetate, i.v.	Same as Trisodium Edetate.
Dithranol Ointment, topical	0.1 per cent.
Strong Dithranol Ointment, topical	1.0 per cent
Doxepin HCl, o.	75-150 mg. p.d. div.
Doxycycline HCl, o.	Equivalent of 200 mg. of doxycycline initially, then equivalent of 100 mg. p.d.
Dydrogesterone, o.	5-30 mg. p.d.
Edrophonium Chloride, i.v.	Initial, 2 mg. Followed by 8 mg. if no response within 30 seconds.
Emetine and Bismuth Iodide, o.	60 to 200 mg. p.d.
Emetine HCl, s.c., i.m.	30 to 60 mg. p.d.
Ephedrine HCl, o.	15 to 60 mg.
Ergometrine Maleate (Ergonovine Maleate)	
o.	0.5 to 1 mg.
i.m.	0.2 to 1 mg.
i.v.	0.1 to 0.5 mg.
Ergotamine Tartrate o.	1 to 2 mg. single dose.
s.c., i.m.	0.25 to 0.5 mg.
Erythromycin, o.	1 to 2 g. p.d. div.
Ethacrynic acid	50-200 mg. p.d. div.
Ethambutol HCl, o	15 to 25 mg./kg. body wt. p.d.
Ethchlorvynol, o.	0.1 to 1 g.
Ethinyloestradiol Tab.	In menopause, 0.01 to 0.05 mg. For suppression of lactation, 0.1 mg. thrice daily for 3 days, followed by 0.1 mg. daily for 6 days. In carcinoma of prostate, 1 to 2 mg. daily.
Ethionamide. o.	0.5 to 1 g. p.d. div.
Ethisterone	25 to 100 mg. daily.
Ethopropazine HCl Tab.	Initial dose 50 mg. Increase gradually to 0.5 g. daily, as per case.
Ethosuximide, o.	500 mg. p.d. div. Increase to 2 g., as per case.
Ethotoin Tab.	1 g. daily. Increase to 3 g., as per case.
Ethyl estranol tab.	2-4 mg. daily.
Ethynodiol diacetate	Progestational steroid (see text).
Fenfluramine Tab.	40 to 80 mg. p.d. div.
Ferric Ammonium Citrate. o.	Upto 6 g. daily, div.
Ferrous Fumarate. o.	Prophylactic, 200 mg. p.d. Therapeutic, 400 to 600 mg. p.d. div.
Ferrous Gluconate. o.	Prophylactic, 600 mg. p.d. Therapeutic, 1.2 to 1.8 g. p.d. div
Ferrous Succinate, o.	Prophylactic, 200 mg. p.d. Therapeutic, 400 to 600 mg. p.d. div.

Official Drug	Dose
Ferrous Sulphate, o.	Prophylactic, 0.3 g. p.d. Therapeutic, 0.6 to 0.9 g. p.d.
Ferrous Sulphate Dried Tab.	Prophylactic, 200 mg. p.d. Therapeutic, 0.4 to 0.6 g. p.d. div.
Fludrocortisone Acetate, o.	In acute adrenocortical insufficiency Initially, 1 to 2 mg. Maintenance, 100 to 200 mcg. p.d.
Fluocinolone Acetonide, topical	0.01 to 0.025 per cent.
Fluocortolone hexanoate	Topical adrenocortical steroid.
Fluocortolone pivalate	Topical adrenocortical steroid.
Fluoxymesterone, o.	1 to 20 mg. p.d.
Fluphenazine HCl	1-2 mg. p.d., single or div. in anxiety states. upto 15 mg. p.d. div. in schizophrenia.
Folic Acid, o.	Therapeutic, 5 to 20 mg. Prophylactic in pregnancy, 0.2 to 0.5 mg. p.d.
Frusemide (Furosemide), o.	40 to 120 mg. p.d
i.m., i.v.	20 to 400 mg.
Gallamine Triethiodide, i.v.	Dose as per need.
Gentamicin Sulphate, i.m.	80,000 to 240,000 Units. p.d. div.
Gentian Infusion Compound Concentrated	1.5 to 4 ml.
Gentian Infusion Compound	15 to 40 ml.
Ginger Tr. Strong	0.25 to 0.5 ml.
Ginger Tr. Weak	1.5 to 3 ml.
Glibenclamide tab.	2.5 to 20 mg. once daily.
Glutethimide, o.	250 to 500 mg.
Glyceryl Trinitrate Tab., sublingual	0.5 to 1 mg.
Griseofulvin Tab.	0.5 to 1 g. p.d. div.
Guanethidine Sulphate Tab.	Initial, 10 to 20 mg. Subsequently increasing to a maximum of 300 mg. daily as per needs.
Halibut Liver Oil	0.2 to 0.5 ml. daily.
Halibut Liver Oil Capsules	1 to 3 capsules daily. (Each containing 4.500 units of vit. A).
Haloperidol, o.	3-9 mg. p.d. div.
Heparin, i.m., i.v.	5,000 to 15,000 units.
Hexylresorcinol	In ascaris infection, Adults. 1 g. as a single dose; Children, 100 mg. for each year of age upto 10 years, as a single dose.
Histamine Acid Phosphate, s.c.	0.5 to 1 mg. (After 5 mg. of antihistamine).
Homatropine Hydrobromide, topical	In eye.
Hyaluronidase	See page 825.
Hydrochloric Acid Dilute	0.5 to 4 ml.
Hydrochlorothiazide, o.	25 to 100 mg.
Hydrocortisone Ointment, topical	1 per cent.
Hydrocortisone Acetate, intra articular	5 to 50 mg.
Hydrocortisone Sodium Succinate, i.v.	Equivalent of 100 to 300 mg. of hydrocortisone, repeated if necessary.
Hydroflumethiazide, o.	25 to 100 mg. p.d.
Hydroxocobalamin, i.m.	In megaloblastic anemia. 1 mg. repeated five times every 2-3 days. Subsequently, 1 mg. every two months.
Hydroxychloroquine Sulphate	For discoid lupus erythematosus and rheumatoid arthritis, 0.2 to 1.2 g. p.d. div. For malaria, suppressive, 400 mg. weekly. Therapeutic, 0.4 to 1.2 g. p.d.

Official Drug	Dose
Hydroxyprogesterone Hexanoate, i.m.	250 to 500 mg. once or twice weekly.
Hyoscine Eye Ointment	0.25 per cent.
Hyoscine Hydrobromide, o., sc.	0.3 to 0.6 mg.
Hyoscyamus Tr.	2 to 5 ml.
Ibuprofen tab.	600 to 1200 mg. p.d. div.
Imipramine HCl, o.	75 to 150 mg. p.d. div.
Indomethacin, o.	75 to 100 mg. p.d. div.
rectally	100 mg. p.d.
Insulin Inj. (Insulin and its various Salts)	See page 713, 717.
Iodine Solution Aqueous	In the preoperative treatment of thyrotoxicosis, 0.1 to 1 ml. p.d.
Ipecacuanha Liquid Extract	0.025 to 0.1 ml.
Ipecacuanha Tr.	0.25 to 1 ml.
Iron Dextran Inj., i.m.	1 to 2 ml. daily.
Iron Sorbitol Inj., i.m.	1 to 2 ml. daily.
Isocarboxazid. o.	Initial, upto 30 mg. daily. Maintenance, 10 to 20 mg. daily.
Isoniazid	300-600 mg. p.d. div.
Isoprenaline Sulphate, sublingual, inhalation	5 to 20 mg.
i.v.	By infusion.
Kanamycin Sulphate, i.m.	0.5 to 1 megaunit p.d. div.
Lanatoside C	Initially 1 to 1.5 mg. maintenance 0.25-0.75 mg. p.d.
Levallorphan Tartrate, i.v.	0.2 to 2 mg.
Levorphanol Tartrate, o.	1.5 to 4.5 mg.
s.c., i.m.	2 to 4 mg.
i.v.	1 to 1.5 mg.
Light Kaolin	15 to 75 g.
Levodopa. o.	Initial 250 mg. p.d. div. Increasing up to 8 gms. p.d. div. as per need.
Lignocaine and Adrenaline Inj.	For local anesthesia, 2 per cent.
Lignocaine Inj., i.v.	100 to 300 mg.
Lincomycin, o., i.m.	Equivalent of 1.5 g. of lincomycin, p.d. div.
Liothyronine Sodium, o.	5 to 100 mcg. daily as per needs.
Liquorice Liquid Extract	2 to 5 ml.
Lithium carbonate	Upto 1.6 g. p.d. div.
Lymecycline, o.	0.8 to 1.6 g. p.d. div.
Lynoestrenol	For oral contraception, 2.5 mg. with an oestrogen.
Magnesium Carbonate, Heavy or Light	As gastric antacid, 250 to 500 mg. As laxative, 2 to 5 g.
Magnesium Oxide Light	As above.
Magnesium Hydroxide Mixture	As antacid, 5 to 10 ml. As laxative, 25 to 50 ml.
Magnesium Sulphate, o.	5 to 15 g.
Magnesium Trisilicate, o.	0.5 to 2 g.
Male Fern Extract	3 to 6 ml. after 24 hrs. starvation.
Mannitol Inj., i.v.	Infusion upto 50 g. on one occasion.
Meclozine HCl. o.	25 to 50 mg. p.d.
Mefenamic acid	0.5 to 1.0 g. p.d. div.
Megestrol acetate	Progestational steroid.
Melarsoprol, i.v.	Adults, Treatment of advanced trypanosomiasis, 0.1 ml./kg. daily for 3 days. Child, 0.05 ml./kg.

Official Drug	Dose
	Repeat the course after 10 days.
Melphalan, o.	2 to 15 mg. p.d.
i.v.	The equivalent of upto 100 mg. of melphalan.
Mepacrine HCl, o.	In malaria, see page 605. In taeniasis, see page 632. In giardiasis, 100 mg. t.i.d.
Mephentermine Sulphate, i.m., i.v. infusion	Equivalent of 20 to 80 mg. base.
Meprobamate, o.	0.4 to 1.2 g. p.d. div.
Mepyramine Maleate, o.	300 to 600 mg. p.d. div.
i.m., i.v.	25 to 50 mg.
Mercaptopurine	100 to 200 mg. daily, div.
Mersalyl, Inj. i.m.	0.5 to 2 ml. on alternate days.
Mestrenol, o.	See page 758.
Metaraminol Tartrate, i.m.	2 to 10 mg.
i.v.	0.5 to 5 mg.
i.v. infusion	100 mg. diluted with atleast 500 ml. of 0.9 per cent saline or 5 per cent dextrose.
Metformin HCl	Initial, 1 to 1.5 g. p.d. div.; subsequently upto 3 g. p.d. div.
Methacycline Cap. o.	0.6 to 1.2 g. p.d. div.
Methadone HCl, o., s.c.	5 to 10 mg.
Methandienone, o.	5 to 10 mg. daily.
Methaqualone	150 to 300 mg.
Methicillin Sodium, i.m.	3 to 6 g. p.d. div.
Methohexitone Sodium, i.v.	30 to 120 mg.
Methoin, o.	100 mg. p.d., increasing to 600 mg., in accordance with the needs of the patient.
Methoserpidine, o.	Initial, 30 mg. p.d. div. Maintenance, upto 60 mg. p.d. div.
Methotrexate, o., i.m. i.v.	5 to 100 mg. at suitable interval.
Methyl Salicylate, topical	See page 131.
Methylamphetamine HCl, o.	2.5 to 10 mg.
i.m., i.v.	10 to 50 mg.
Methyldopa, o.	0.5 to 3 g. p.d., div.
i.v.	250-500 mg.
Methylene Blue, i.v.	1 to 4 mg./kg.
Methylergometrine Maleate, o.	0.25 to 0.5 mg.
s.c., i.m. i.v.	0.1 to 0.2 mg.
Methylprednisolone, o.	8 to 80 mg. p.d. div.
Methyltestosterone, o.	Men, 25 to 50 mg. p.d. Women, 5 to 20 mg. p.d. In mammary carcinoma, 50 to 100 mg. p.d.
Methylthiouracil, o.	Controlling dose, 200 to 600 mg. p.d. Maintenance dose, 50 to 200 mg. p.d.
Methyprylone, o.	200 to 400 mg. p.d. div.
Metronidazole, o.	600 mg. p.d. div. for 7 days. In amebiasis 1.2 to 2.4 g. daily div. for 5-10 days.
Morphine HCl	10 to 20 mg.
Morphine Sulphate, o., s.c., i.m.	10 to 20 mg.
Mustine HCl, i.v.	0.4 mg./kg. as a single dose or divided doses over 4 days.
Nalorphine Hydrobromide, i.v.	In poisoning by morphine, 5 to 10 mg. repeated as per case to a maximum total of 40 mg.
Nandrolone Decanoate, i.m.	25 to 50 mg. as per case.

Official Drug	Dose
Nandrolone Phenylpropionate, i.m.	25 to 50 mg. weekly.
Naphazoline Nitrate	Topical.
Neomycin Sulphate	As intestinal antiseptic, 2 to 8 megaunits p.d. div.
Neostigmine Bromide Tab.	15 to 30 mg. as per case.
Neostigmine Methylsulphate, s.c. i.m	0.5 to 2 mg. as per case.
Nialamide, o.	Initial, 150 mg. p.d. div. Maintenance, 75 mg. p.d. div, or as per case.
Niclosamide, o.	2 g. div.
Nicotinamide, i.v.	50 to 250 mg.
o.	Prophylactic, 15 to 30 mg. p.d. Therapeutic, 50 to 250 mg.
Nicotinic Acid, o.	Prophylactic, 15 to 30 mg. Therapeutic, 50 to 250 mg.
Nicoumalone, o. (Acenocoumarol)	As anticoagulant: Initial, 12 to 20 mg. Subsequently 2-12 mg. as per prothrombin activity.
Nikethamide, i.v.	2 to 8 ml. repeated if necessary.
Nitrazepam	5 to 10 mg. p.d.
Nitrofurantion	50 to 150 mg. 4 times a day.
Noradrenaline Acid Tartrate	2 to 20 mcg. per minute by infusion.
Norethandrolone, o.	25 to 50 mg. per day.
Norethisterone, o.	5 to 20 mg. p.d. single or div.
Norethisterone Acetate, o.	2.5 to 20 mg. p.d. in single or div. doses.
Norethynodrel, o.	5 to 30 mg. daily.
Nortriptyline HCl, o.	20 to 100 mg. p.d. div.
Noscapine, o.	15 to 30 mg.
Novobiocine Calcium or Sodium, o.	1 to 2 g. p.d. div.
Nux Vomica Liquid Extract	0.05 to 0.2 ml.
Nux Vomica Tr.	0.5 to 2 ml.
Nystatin	In the treatment of alimentary moniliasis, 1 to 2 megaunits p.d. div.
Oestradiol Benzoate, i.m.	1 to 5 mg. daily.
Opium Tr., o.	0.25 to 2 ml.
Opium Tr. Camphorated, o.	2 to 10 ml.
Opium, powdered	25 to 200 mg.
Orciprenaline Sulphate, o.	20 to 80 mg. p.d. div. or in single dose.
s.c., i.m.	0.5 mg.
Orphenadrine Citrate or HCl, o.	200 to 400 mg. p.d. div.
Oxyphenbutazone, o.	200 to 400 mg. p.d. div.
Oxyphencyclimine HCl, o.	As parasympatholytic antispasmodic, 15 to 20 mg. p.d. div.
Oxprenolol tab.	0.04 to 2 g. p.d. div.
Oxytetracyline HCl, o. i.v.	0.1 per cent w/v, not exceeding 1 to 2 g. daily, by i.v. infusion. 1-3 g. p.d. div. o.
Oxytocin Inj. i.v. infusion	For induction of labour, 2 to 5 units in 1000 ml. of 5 per cent dextrose. For stimulation of uterine contraction during labour 1 to 5 units in 1000 ml. of 5 per cent. dextrose.
s.c., i.m., slow i.v.	Post-partum haemorrhage, 2 to 5 units.
Oxytocin Tab.	As per case.
Pancreatin	1 to 6 g. p.d. with meals.
Papaverine HCl, s.c.	60 to 300 mg.
Paracetamol, o.	0.5 to 1 g., upto 4 g. p.d. div.

Official Drug	Dose
Paraffin Liquid	10 to 30 ml.
Paraldehyde, o., i.m.	5 to 10 ml.
Paramethadione, o.	See page 109.
Penicillamine, o.	0.5 to 1.5 g. p.d. div. as per case.
Pentaerythritol Tetranitrate, o.	10 to 30 mg.
Pentamidine Isethionate, i.m.	In the treatment of trypanosomiasis. Prophylactic, 300 mg. every 3 to 6 months. In early trypanosomiasis and leishmaniasis, 150 to 300 mg. p.d. for 7 to 15 days.
Pentazocin, o.	25 to 100 mg.
Pentazocin lactate i.m., i.v.	Equivalent to 30 to 60 mg. of pentazocin.
Pentobarbitone Sodium Tab.	0.1 to 0.2 g.
Pentolinium Tartrate, s.c.	Initial, 1 mg. Subsequently, increased as per case.
Peppermint Oil, o.	0.05 to 0.2 ml.
Perphenazine	As antiemetic, 4 to 8 mg. In psychiatric state, 8 to 24 mg. p.d. div.
Pethidine HCl, o.	50 to 100 mg.
s.c., i.m.	25 to 100 mg.
i.v.	25 to 50 mg.
Phenacetin Tab.	0.3 to 0.6 g. single dose.
Phenazocine HBr.	5 to 20 mg., I.M.: 1-3 mg., I.V.: 0.5 to 1 mg.
Phenelzine Sulphate	15 to 45 mg. of base p.d.
Phenethicillin Potassium, o.	0.5 to 1.5 g. p.d. div.
Phenformin Tab.	50 to 200 mg. p.d. div.
Phenindamine Tartrate, o.	75 to 150 mg. p.d. div.
Phenindione, o.	Initial 0.2 to 0.3 g. Subsequently, 25 to 100 mg. daily.
Phenmetrazine HCl, o.	25 to 75 mg. p.d. div.
Phenobarbitone and Phenobarbitone Sodium, o.	Upto 350 mg. daily div.
s.c., i.m. i.v.	50 to 200 mg. as a single dose.
Phenolphthalein Tab.	50 to 300 mg. (To be chewed before swallowing).
Phenoxybenzamine HCl, o.	Initial, 10 to 20 mg. Subsequently, increased as per case.
Phenoxymethylpenicillin (Penicillin V) Tab.	0.5 to 1.5 g. p.d. div.
Phenoxymethylpenicillin Calcium or Potassium Salt, o.	0.5 to 1.5 g. p.d. div.
Phentolamine Mesylate i.v.	5 to 10 mg.
Phenylbutazone, o.	200 to 400 mg. p.d. div.
Phenylephrine HCl, i.v.	0.5 mg.
s.c., i.m.	5 mg.
Phenytoin Sodium Tab.	50 mg. increased as per needs to 200 mg.
Pholcodine, o.	Upto 60 mg. p.d. div.
Phthalylsulphathiazole Tab.	5 to 10 g. p.d. div.
Physostigmine Salicylate	topical
Phytomenadione, (Vitamin Kl) s.c., i.m. i.v.	5 to 20 mg. repeated as per need. In new born 0.5 to 1 mg.
Pilocarpine Nitrate	topical
Piperazine adipate, citrate and phosphate, o.	See page 634, 638.
Poldine Methylsulphate, o.	10 to 30 mg. p.d. div.
Polymixin B. Sulphate, o.	1 to 2 mega units p.d. div.
i.m.	500,000 units every 8 hrs
Potassium Bromide, o.	1 to 6 g. p.d. div.
Potassium Chloride, o. i.v.	As per need.
Potassium Citrate, o.	Upto 10 g. p.d. div.

Official Drug		Dose
Potassium Iodide, o.	:	As expectorant, 250 to 500 mg. In the pre-operative treatment of thyrotoxicosis, 150 mg. p.d. div.
Practolol, o.	:	200 to 900 mg. p.d. div.
i.v.	:	Slow Inj., 5 to 20 mg.
Prednisolone or Its Acetate Tab.	:	10 to 100 mg. p.d. div.
Prednisolone Pivalate, intra-articular inj. or local infiltration	:	5 to 20 mg.
Prednisolone Sodium Phosphate, i.v.	:	The equivalent of 20 to 100 mg. of prednisolone.
Prednisone or Its Acetate Tab.	:	10 to 100 mg. p.d. div.
Primaquin Phosphate	:	See page 605.
Primidone Tab.	:	Initial, 0.5 g. p.d. Increasing to 2 g. as per needs.
Probenecid, o.	:	1 to 2 g. daily.
Procainamide HCl, slow i.v.	:	Upto 1 g. of a 2.5 per cent w/v solution, the amount determined by the effects produced.
o.	:	0.5 to 1.5 g.
Procaine HCl	:	See page 313.
Procaine Penicillin, i.m.	:	300 to 900 mg. p.d. div.
Procaine Penicillin Fortified, i.m. (300 mg. of Procaine Penicillin and 60 mg. of Benzyl Penicillin)	:	As per need (see text).
Prochlorperazine Maleate, o.	:	As antiemetic, 10 to 30 mg. In psychiatric state, 15 to 100 mg. p.d. div.
Prochlorperazine Mesylate, i.m.	:	Antiemetic, 12.5 mg. In psychiatric state, 12.5 to 25 mg. two or three times daily.
Procyclidine HCl Tab.	:	Initial, 7.5 mg. div. Increasing gradually to 30 mg. p.d. as per case
Progesterone, i.m.	:	20 to 60 mg. p.d.
Proguanil HCl, o.	:	Suppressive of malaria, 0.1 to 0.3 g. p.d.
Promazine HCl, o., i.m., i.v.	:	50 to 800 mg. p.d. div.
Promethazine HCl, o., i.m.	:	20 to 50 mg. p.d. single or div.
Promethazine Theoclate, o.	:	25 to 50 mg. p.d. single or div.
Propantheline Bromide Tab.	:	Up to 45 mg. p.d. div.
Propicillin Tab.	:	0.5 to 1.5 g. propicillin p.d. div.
Propranolol HCl, o.	:	20 to 400 mg. p.d. div. The initial dose should not exceed 120 mg.
slow i.v.	:	3 to 10 mg.
Propylthiouracil Tab.	:	Controlling dose, 0.2 to 0.6 g. p.d. Maintenance dose, 50 to 200 mg. p.d.
Protamine Sulphate, i.v.	:	As per needs.
Protriptyline Tab.	:	15 to 60 mg. p.d. div.
Pseudoephedrine HCl	:	60 to 180 mg. p.d. div.
Pyrazinamide, o.	:	Upto 35 mg./kg. div.
Pyridostigmine Bromide, o.	:	In the treatment of myesthenia gravis, 60 to 240 mg., repeated as per case.
Pyridoxine HCl, s.c., i.m.	:	Deficiency anemia in adults, 150 mg. p.d. div.
Pyrimethamine Tab.	:	As suppressive of malaria, 25 to 50 mg. weekly.
Quinalbarbitone Sodium, o.	:	0.1 to 0.2 g.
Quinidine Sulphate, o., i.m.	:	Prophylaxis of cardiac arrhythmias, 200 mg. 3 to 4 times p.d. In atrial fibrillation, 200 to 400 mg. every 2 to 4 hrs. to a total dose of 3 g. daily.

Official Drug	Dose
Quinine Sulphate, Quinine Bisulphate	In suppression of malaria, 0.3 to 0.6 g. p.d.
Quinine HCl, Quinine Dihydrochloride	In treatment of malaria, 1.2 to 2 g. p.d. div.
Quinine Dihydrochloride, slow i.v.	300 to 600 mg.
Reserpine Tab.	In hypertension, 0.1 to 0.5 mg. p.d. div. In psychiatric states, 1 to 5 mg. p.d. div.
Rhubarb, o.	0.2 to 1 g.
Rhubarb Compound Tr.	Upto 15 ml. p.d. div.
Riboflavin Tab.	Prophylactic, 1 to 4 mg. p.d. Therapeutic, 5 to 10 mg. p.d.
Salbutamol Tab.	Equivalent of 6 to 16 mg. of salbutomol p.d. div.
Salicylic Acid Ointment, topical	2 per cent
Senna Fruit, o.	0.5 to 2 g.
Sodium Aminosalicylate Tab.	10 to 15 g. p.d. div.
Sodium Aurothiomalate, i.m.	10 mg., increasing gradually to 100 mg. weekly. The total dose in a course should not exceed 1 g.
Sodium Bicarbonate	1 to 5 g. o., 1.4 per cent w/v as per case, i.v.
Sodium Bromide, o.	1 to 6 g. p.d. div.
Sodium Calciumedetate, o.	In lead poisoning, upto 4 g. of anhydrous salt p.d. div.
i.v.	A maximum of 40 mg./kg. over a period of one hour twice daily upto 5 days.
Sodium Chloride, i.v.	0.9 per cent as per case.
Sodium Citrate, o.	Upto 10 g. p.d. div.
Sodium Cromoglycate	as cartridges, used by inhalation.
Sodium Fusidate, o.	1 to 2 g. p.d. div.
Sodium Iodide, o.	As expectorant, 0.25 to 0.5 g. In thyrotoxicosis, pre-operative, upto 150 mg. p.d. div.
Sodium Phosphate (^{32}P) Inj., i.v.	In the treatment of polycythaemia vera. Initially, 5 millicuries. Followed by 3 millicuries after 3 months, as per needs.
Sodium Salicylate, o.	In acute rheumatism, 5 to 10 g. p.d. div.
Sodium Stibogluconate, i.m., i.v.	0.6 to 2 g. p.d. for 10 to 30 days.
Sodium Sulphate, o.	5 to 15 g. (as purgative).
Sorbitol i.v.	Upto 0.6 g. per min.
Spironolactone, o.	100 to 200 mg. p.d. div.
Stilboestrol	In menopause, 0.1 to 1 mg. For suppression of lactation, 5 mg., thrice daily for 3 days, followed by 5 mg. daily for 6 days. In carcinoma of prostate and breast, 10 to 20 mg. p.d.
Stramonium Tr.	Upto 6 ml. p.d. div.
Streptomycin Sulphate, o.	Intestinal antiseptic, 500 mg. of the base 8 hrly.
i.m.	0.5 to 1 g. of the base daily or at longer intervals.
Succinylsulphathiozole, o.	10 to 20 g. p.d. div.
Sulphacetamide Eye Ointment, topical	6 per cent.
Sulphadiazine Tab.	In systemic infections, initial, 3 g. Subsequently, upto 4 g. p.d. div.
Sulphadiazine Sodium, i.v., i.m.	Equivalent to 1 to 2 g. of Sulphadiazine.
Sulphadimethoxine, o.	Initial, 1 to 2 g. Subsequently, 500 mg. daily.
Sulphadimidine Tab.	In urinary tract infection, initial, 2 g. Subsequently, upto 4 g. p.d. div.

Official Drug		Dose
		In systemic infection, initial, 3 g. Subsequently, 6 g. p.d. div.
Sulphadimidine Sodium, i.m., i.v.	:	1 to 2 g.
Sulphafurazole, o.	:	In systemic infections, initial, 3 g. Subsequently, upto 6 g. div. In urinary tract infection, initial, 2 g. Subsequently, upto 4 g. p.d. div.
Sulphamethizole, o.	:	100 to 200 mg. every 4 to 6 hrs.
Sulphamethoxazole	:	used in co-trimoxazole.
Sulphamethoxydiazine, o.	:	Initial, 1 to 2 g. Subsequently, 500 mg. p.d.
Sulphamethoxypyridazine, o.	:	Initial, 1 g. Subsequently, 500 mg. p.d.
Sulphinpyrazone, o.	:	200 to 500 mg. p.d. div,
Sulphomyxin Sodium, i.m. (Mixture of Sulphomethylated Polymixin B and Sodium Bisulphite).	:	Upto 2 megaunits p.d. div.
Sulphur Ointment, topical	:	10 per cent.
Sulthiame, o.	:	Upto 600 mg. p.d. div.
Suxamethonium Bromide or Chloride, i.v.	:	as per needs.
Testosterone, implantation	:	Total dose, 0.1 to 0.6 g.
Testosterone Phenyl Propionate, i.m.	:	5 to 25 mg. once or twice weekly.
Testosterone Propionate, i.m.	:	5 to 25 mg. once or twice weekly.
Tetrachloroethylene, o.	:	1 to 3 ml. Single dose.
Tetracosactrin Acetate, i.m., i.v.	:	0.25 mg.
Tetracosactrin Zn-inj. s.c., i.m.	:	0.5 to 2 mg. of tetracosactrin.
Tetracycline HCl, o.	:	1 to 3 g. p.d. div.
i.v. infusion	:	Concentration not exceeding 0.1 per cent w/v, 1 to 2 g., p.d.
Thiambutosine, o.	:	In leprosy, 500 mg. p.d., increasing by 500 mg. every 14 days, upto 2 g. p.d. div.
Thiamine HCl, o., s.c., i.m.	:	Prophylactic, 2 to 5 mg. p.d. Therapeutic, 25 to 100 mg. p.d.
Thiopentone Sodium, i.v.	:	0.1 to 0.5 g.
Thioridazine HCl, o.	:	30 to 600 mg. p.d. div.
Thiotepa	:	I.V.—15 to 30 mg. repeated as per needs; into serous cavities, 45 to 60 mg. repeated as per needs.
Thyroid Extract Tab.	:	30 to 250 mg. p.d.
Thyroxine Sodium, o.	:	0.05 to 0.3 mg. p.d.
Tolazoline HCl, o., i.v.	:	Upto 200 mg. p.d. div.
Tolbutamide, o.	:	0.5 to 1.5 g. p.d.
Tolnaftate	:	Topical in fungal infections.
Tranylcypromine Sulphate, o.	:	Initial, equiv. of 20 mg. of base p.d. div. Subsequently, as per case.
Triamcinolone Acetonide	:	Topical
Triameterene, o.	:	150 to 250 mg. p.d. div.
Triclofos Sodium, o.	:	0.5 to 2 g. as a single dose.
Trifluoperazine HCl, o.	:	In psychiatric state, 2 to 30 mg. p.d. div. Anti-emetic, 1 to 6 mg. p.d.
Trimethoprim	:	In co-trimoxazole tab.
Triimipramine tab.	:	25 to 125 mg. p.d. div.
Triprolidine HCl, o.	:	5 to 7.5 mg. p.d. div.
Trisodium Edetate, i.v. infusion	:	Not exceeding equiv. of 70 mg./kg. base.
Troxidone, o.	:	Adult 0.9 to 1.8 g. p.d. div. Child 0.3 to 0.9 g. p.d. div.
Tubocurarine Chloride, i.v.	:	As per needs.

Official Drug		Dose
Urea, i.v. infusion	:	30 per cent w/v solution, 40 to 80 g. but not exceeding 1.5 g./kg. in 24 hrs.
Vancomycin HCl, i.v. slow inj.	:	0.5 per cent w/v, 1 to 2 megaunits p.d. div. or single.
Vasopressin, s.c., i.m.	:	2 to 20 units (0.1 to 1.0 ml.).
Vinblastin inj. i.v.	:	Upto 10 mg. weekly.
Vincristine i.v.	:	Adult 25-75 micro-g./kg. weekly. Child 30-150 micro-g./kg. weekly.
Viomycin Sulphate, i.m.	:	0.5 to 1 megaunit daily or at longer intervals.
Viprynium Embonate, o.	:	5 mg./kg. single dose.
Vitamin A Ester Concentrate, o. (485,000 units of vit. A activity/g)	:	See page 830.
Warfarin Sodium	:	Initial, 30 to 50 mg. Subsequently, 3 to 10 mg. daily as per prothrombin time.

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